Subject request from Cornell

From Valerie Cross Dorn <vlc1@cornell.edu>

To: matzirvi@yahoo.com <matzirvi@yahoo.com>

Cc: Pearson, Matthew <mpearson@akingump.com>

Date Feb 24, 2015 at 9:50 AM

Dear Dr. Zirvi,

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Associate University Counsel
Cornell University
[redacted]

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AKIN GUMP STRAUSS HAUER & FELD LLP
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From Monib Zirvi <matzirvi@yahoo.com>

To: Valerie Cross Dorn <vlc1@cornell.edu>

Cc: Pearson, Matthew <mpearson@akingump.com>

Date Feb 24, 2015 at 10:09 AM

Dear Valerie and Matthew,

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Sent from my iPhone

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From Pearson, Matthew <mpearson@AKINGUMP.com>

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Date Feb 25, 2015 at 11:34 AM

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From Pearson, Matthew <mpearson@AKINGUMP.com>

To: Monib Zirvi <matzirvi@yahoo.com>

Cc: Valerie Cross Dorn <vlc1@cornell.edu>

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Cc: Valerie Cross Dorn <vlc1@cornell.edu>

Date May 14, 2015 at 7:03 AM

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Subject Fwd: Current CV

From Monib Zirvi <matzirvi@yahoo.com>

To: Matthew Pearson <mpearson@akingump.com>

Bcc: Abu <matzirvi@yahoo.com>

Date May 18, 2015 at 1:18 PM

Dear Matt,

Here is my CV.

All the best,

Monib Zirvi

Sent from my iPhone

Begin forwarded message:

> **From:** "Zirvi, Monib MD" <MZirvi@smgnj.com>
> **Date:** May 18, 2015 at 1:15:13 PM EDT
> **To:** "matzirvi@yahoo.com" <matzirvi@yahoo.com>
> **Subject: Current CV**

Attached is the current CV.

This e-mail may contain confidential or privileged information. If you are not the intended recipient, please advise the sender by reply e-mail and then delete this e-mail immediately.

View less

MonibZirviCV2015.doc

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Sent from my iPhone

Begin forwarded message:

> **From:** "Zirvi, Monib MD" <MZirvi@smgnj.com>
> **Date:** May 18, 2015 at 1:15:13 PM EDT
> **To:** "matzirvi@yahoo.com" <matzirvi@yahoo.com>
> **Subject: Current CV**
>
> Attached is the current CV.
>
> This e-mail may contain confidential or privileged information. If you are not the intended recipient, please advise the sender by reply e-mail and then delete this e-mail immediately.

MonibZirviCV2015.doc

Subject RE: Current CV

From Pearson, Matthew <mpearson@AKINGUMP.com>

To: Monib Zirvi <matzirvi@yahoo.com>

Date May 18, 2015 at 5:44 PM

Dr. Zirvi –

I just got back to my desk – I have it. Thanks.

From: Monib Zirvi [mailto:matzirvi@yahoo.com]
Sent: Monday, May 18, 2015 5:27 PM
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Thank you.

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View less

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To: Pearson, Matthew
Subject: Fwd: Current CV

Dear Matt,

Here is my CV.

All the best,

Monib Zirvi

Sent from my iPhone

Begin forwarded message:

From: "Zirvi, Monib MD" <MZirvi@smgnj.com>
Date: May 18, 2015 at 1:15:13 PM EDT
To: "matzirvi@yahoo.com" <matzirvi@yahoo.com>
Subject: Current CV

Attached is the current CV.

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View less

Subject Automatic reply: Current CV

From Pearson, Matthew
<mpearson@AKINGUMP.com>

To: Monib Zirvi <matzirvi@yahoo.com>

Date May 21, 2015 at 10:21 AM

I am traveling until May 25 and may have limited access to email at times. I will respond to your message as soon as I can. If this is an emergency, please contact Marci Weinstein, mweinstein@akingump.com.

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Subject RE: Current CV

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View less

Subject RE: Current CV

From Pearson, Matthew <mpearson@AKINGUMP.com>

To: Monib Zirvi <matzirvi@yahoo.com>

Date May 22, 2015 at 10:41 AM

Thank you – we'll plan on Wednesday

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Date May 27, 2015 at 7:57 AM

Sorry for the late notice – but I need to postpone our call. Would Friday work? We could set the same time, or most other times (my Friday is very open).

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Dear Matt,

Here is my CV.

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Monib Zirvi

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Subject Re: Current CV

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Date May 27, 2015 at 8:29 AM

In the morning on Friday around 10 am works best.

Monib

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All the best,

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View less

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To: Monib Zirvi <matzirvi@yahoo.com>

Date May 27, 2015 at 8:31 AM

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To: Monib Zirvi <matzirvi@yahoo.com>

Date Jun 25, 2015 at 8:01 AM

Dr. Zirvi –

Thanks for your patience. We have confirmed that your deposition will be July 11. So we should plan for a two day stay, a preparation day on July 10 followed by the deposition day.

Please let me know if our staff can help with travel or hotel arrangements – they will have hotel recommendations, and can help with logistics.

And please don't hesitate to contact me with any questions. (I will be traveling over the next couple of days, so I apologize in advance for any delays in my response).

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Sent: Monday, May 18, 2015 1:19 PM
To: Pearson, Matthew
Subject: Fwd: Current CV

Dear Matt,

Here is my CV.

All the best,

Monib Zirvi

Sent from my iPhone

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> **From:** "Zirvi, Monib MD" <MZirvi@smgnj.com>
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To: Monib Zirvi <matzirvi@yahoo.com>

Date Jun 25, 2015 at 4:50 PM

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>>
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>>
>> Best,
>>
>> Matt

Matthew A. Pearson
AKIN GUMP STRAUSS HAUER & FELD LLP
[redacted]

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> Matt
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Best,
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All the best,

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Subject Re: Current CV

From Monib Zirvi <matzirvi@yahoo.com>

To: Pearson, Matthew <mpearson@AKINGUMP.com>

Date Jun 25, 2015 at 6:47 PM

Thank you. I booked a room at the Ritz-Carlton like you suggested.

Sincerely,

Monib

Sent from my iPhone

On Jun 25, 2015, at 4:50 PM, Pearson, Matthew <mpearson@AKINGUMP.com> wrote:

Yes - our office is the location for both days.

We should plan for a 9:30 start for the prep day. The deposition day will start a little earlier, just so we can get settled before starting at 9 or 9:30.

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And please don't hesitate to contact me with any questions. (I will be traveling over the next couple of days, so I apologize in advance for any delays in my response).

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Subject Private Re: Discovery of streptomycin -- and who claimed credit

From Francis Barany <barany@med.cornell.edu>

To: Valerie Cross <vlc1@cornell.edu>, Pearson, Matthew <mpearson@AKINGUMP.com>, Weil, Jason <jweil@akingump.com>, delderkin@akingump.com <delderkin@akingump.com>, Brian Kelly <bjk44@cornell.edu>

Cc: Verrecchio, Angela <averrecchio@akingump.com>, Robert Hammer <rphammer@gmail.com>, George Barany <barany@umn.edu>, Monib Zirvi <matzirvi@yahoo.com>

Date Oct 21, 2015 at 11:00 AM

Dear Valerie, Matthew, Jason, Diane, and Brian,

Please see the link Bob Hammer sent below about the fight for credit to the discovery of Streptomycin…

http://www.nytimes.com/2012/06/12/science/notebooks-shed-light-on-an-antibiotic-discovery-and-a-mentors-betrayal.html?_r=0

In case you never heard of this story, the NYTimes gets it right...

A fictionalized version of the race to discover and commercialize antibiotics is provided in the novel "A Fierce Radiance" by Lauren Belfer, told with the Rockefeller Institute as the backdrop for these discoveries — George and I were both graduate students at Rockefeller in the late 1970's.

(Link to book on Amazon, below),

All the best,

Francis

Francis

[redacted]

A Fierce Radiance: A Novel Paperback – March 29, 2011

by Lauren Belfer

http://www.amazon.com/Fierce-Radiance-Novel-Lauren-Belfer/dp/0061252522/ref=sr_1_1?s=books&ie=UTF8&qid=1445439107&sr=1-1&keywords=a+fierce+radiance+by+lauren+belfer

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Begin forwarded message:

Date: October 21, 2015 at 9:56:43 AM EDT
Subject: streptomycin
From: Robert Hammer <rphammer@gmail.com>
To: Francis Barany <barany@med.cornell.edu>, George Barany <barany@umn.edu>, "Verrecchio, Angela" <Averrecchio@akingump.com>

http://www.nytimes.com/2012/06/12/science/notebooks-shed-light-on-an-antibiotic-discovery-and-a-mentors-betrayal.html?_r=0

you probably know the story well.

I watched "American Experience" last night about "the Forgotten Plague" of TB

Cool story. They didn't delve into the Waksman and Schatz too much. the above article was interesting take on it all.

Subject Privileged and Confidential

From Monib Zirvi <matzirvi@yahoo.com>

To: <mpearson@akingump.com>

Date Oct 31, 2015 at 12:39 PM

Dear Matthew,

As my attorney, this communication is protected due to Attorney-Client Priviledge. I just want to let you know that I agree with Francis wholeheartedly that the plagiarized zipcode sequences in the Illumina are a critical piece of evidence to show to a Jury to demonstrate a deliberate and willful intent to circumvent existing patents by filing almost identical patents by the defendant. This is a repeated offense by Illumina as they have already been shown to have done this before. I understand that the application never issued, but it shows how underhanded they are in terms of paying rightful royalties that other companies have paid during the period I question.

Please discuss this with Francis after having read the document that was prepared.

Sincerely yours,

Dr. Monib Zirvi, MD/PhD
Cornell University Medical College

Sent from my iPhone

Subject Priviledged and Confidential

From Monib Zirvi <matzirvi@yahoo.com>

To: <mpearson@akingump.com>

Date Oct 31, 2015 at 12:41 PM

Dear Matthew,

As my attorney, this communication is protected due to Attorney-Client Priviledge. I just want to let you know that I agree with Francis wholeheartedly that the plagiarized zipcode sequences in the Illumina patent application are a critical piece of evidence to show to a Jury to demonstrate a deliberate and willful intent to circumvent existing patents by filing almost identical patents by the defendant. This is a repeated offense by Illumina as they have already been shown to have done this before. I understand that the application never issued, but it shows how underhanded they are in terms of trying to avoid paying rightful royalties that other companies have paid during the period in question.

Please discuss this with Francis after having read the document that was prepared.

Sincerely yours,

Dr. Monib Zirvi, MD/PhD
Cornell University Medical College

Sent from my iPhone

Subject Re Privileged and Confidential webex Nov. 5, 10:00 AM: '917 Patent & Zip codes - Pearson - Cross-Dorn - Weil

From Francis Barany <barany@med.cornell.edu>

To: Pearson, Matthew <mpearson@AKINGUMP.com>, Weil, Jason <jweil@akingump.com>, Valerie Cross <vlc1@cornell.edu>, Monib Zirvi <matzirvi@yahoo.com>

Cc: Francis Barany <barany@med.cornell.edu>

Date Nov 3, 2015 at 11:45 AM

Dear Matthew et. al,

As per your instructions below, looking forward to our weber discussion on Thursday, November 5th & 10:00 AM.

All the best,

Francis

[redacted]

On Nov 2, 2015, at 10:35 PM, Pearson, Matthew <mpearson@AKINGUMP.com> wrote:

Francis -

Thursday morning will work from 10 to 11. Tomorrow or Wednesday will not work.

Regards,
Matt

Sent from my iPhone

Begin forwarded message:

Date: November 3, 2015 at 11:41:55 AM EST
From: Francis Barany <messenger@webex.com>

From: Francis Barany <messenger@webex.com>
Reply-To: <barany@med.cornell.edu>
To: <barany@med.cornell.edu>
Subject: (Forward to others) WebEx meeting invitation: '917 Patent & Zip codes - Pearson - Cross-Dorn - Weil

You can forward this invitation to others.
Hello,

Francis Barany invites you to join this WebEx meeting.

'917 Patent & Zip codes - Pearson - Cross-Dorn - Weil
Thursday, November 5, 2015
10:00 am | Eastern Standard Time (New York, GMT-05:00) | 1 hr

Join WebEx meeting
Meeting number: [redacted]
Meeting password: [redacted]

Join by phone
[redacted]

Add this meeting to your calendar.

Can't join the meeting? Contact support.

IMPORTANT NOTICE: Please note that this WebEx service allows audio and other information sent during the session to be recorded, which may be discoverable in a legal matter. By joining this session, you automatically consent to such recordings. If you do not consent to being recorded, discuss your concerns with the host or do not join the session.

Subject Confidential: 1536 beads, but only use 1520 zip codes

From Francis Barany <barany@med.cornell.edu>

To: Pearson, Matthew <mpearson@AKINGUMP.com>

Cc: Monib Zirvi <matzirvi@yahoo.com>, Valerie Cross <vlc1@cornell.edu>

Date Nov 5, 2015 at 1:02 PM

Dear Matthew,

Thanks again for your patience this morning. I apologize again that we came across as upset — we are not upset with you — just that we are very passionate about our work.

I did go back and found the paper by Gunderson et-al 2004 (enclosed). By that point they were already using zip-codes in the size range of 22-24 (perhaps someone told them to "mix in some 22-mers and 23-mers with the 24-mers, to get around Barany's patents"), but it doesn't matter, as the 22-mers most-likely differed from each other and other sequences by 6 or more bases (based on probability alone).

They claim to synthesize 1536 beads, with 16 of the bead types discarded due to low signal-to-noise ratios. It would be interesting to understand why these 16 failed, was there anything wrong with their sequence design, their synthesis, real Tm lower than calculated Tm — or were they discarded for "another" reason?

Again, please let us know how we can be of further assistance.

All the best,

Francis

[redacted]

METHODS

Preparation of Oligonucleotide-Linked Beads and Bead Pools

A set of 1536 universal capture oligonucleotide sequences was synthesized. Each sequence was individually immobilized on activated beads, as follows, to create 1536 bead types. Silica beads ~3 μm in diameter (Bangs Laboratories, Inc.) were amino functionalized by incubation in 2.5% 3-amino-propyl-trimethoxysilane (Aldrich) in ethanol for 1 h at RT and then activated by reaction with 2% 2,4,6-trichloro-1,3,5-triazine (Aldrich) in acetonitrile for 2 h at room temperature. Synthetic oligonucleotides labeled at the 5 terminus with a primary amine were covalently attached to the activated beads by overnight reaction at 50°C in a solution of 3 M NaCl and 100 mM sodium carbonate (pH 11). All reagents were of highest purity grade. Empirical measurements indicated that, on average, each bead carried on the order of 106 oligonucleotides. Following quality assessment, 16 of the bead types were discarded due to low signal-to-noise ratios. The remaining bead types were combined to create a pool containing 1520 functional bead types, each representing a unique capture sequence. The sequences were designed to serve as noninteracting decodable address sequences in addition to their function as probes that capture assay products from solution. They were selected to be 22 to 24 bases long with minimal crosscomplementarity, similar GC content and Tm, no runs of a single base longer than five, and low similarity to human genomic sequences.

ATT00001.htm

Decoding Randomly Ordered DNA Arrays

Kevin L. Gunderson,[1,3] Semyon Kruglyak,[1,3] Michael S. Graige,[1] Francisco Garcia,[1] Bahram G. Kermani,[1] Chanfeng Zhao,[1] Diping Che,[1] Todd Dickinson,[1] Eliza Wickham,[1] Jim Bierle,[1] Dennis Doucet,[1] Monika Milewski,[2] Robert Yang,[1] Chris Siegmund,[1] Juergen Haas, Lixin Zhou,[1] Arnold Oliphant,[1] Jian-Bing Fan,[1] Steven Barnard,[1] and Mark S. Chee[1,4]

[1]Illumina, Inc., San Diego, California 92121, USA; [2]Genomics Institute of the Novartis Research Foundation, San Diego, California 92121, USA

We have developed a simple and efficient algorithm to identify each member of a large collection of DNA-linked objects through the use of hybridization, and have applied it to the manufacture of randomly assembled arrays of beads in wells. Once the algorithm has been used to determine the identity of each bead, the microarray can be used in a wide variety of applications, including single nucleotide polymorphism genotyping and gene expression profiling. The algorithm requires only a few labels and several sequential hybridizations to identify thousands of different DNA sequences with great accuracy. We have decoded tens of thousands of arrays, each with 1520 sequences represented at ~30-fold redundancy by up to ~50,000 beads, with a median error rate of $<1 \times 10^{-4}$ per bead. The approach makes use of error checking codes and provides, for the first time, a direct functional quality control of every element of each array that is manufactured. The algorithm can be applied to any spatially fixed collection of objects or molecules that are associated with specific DNA sequences.

Microarray technology, devised for the analysis of complex biological systems, uses the ability of a DNA strand to hybridize specifically to its complement to extract 1000s of measurements at a time from a single sample (Watson and Crick 1953; Southern et al. 1992; Pease et al. 1994; Schena et al. 1995; Chee et al. 1996; Lockhart et al. 1996; Lockhart and Winzeler 2000). Although relatively new, this technology has enabled a variety of important applications, for example, genome-wide quantitative analysis of gene expression and large-scale single nucleotide polymorphism (SNP) discovery and genotyping (Chee et al. 1996; Lockhart et al. 1996; Wang et al. 1998; Fan et al. 2003; Hardenbol et al. 2003; Kennedy et al. 2003; Yvert et al. 2003). Microarrays are also beginning to play a role in the reinvention of cancer classification and drug discovery (Johnson et al. 2002; van't Veer et al. 2002).

Conventional microarrays are manufactured by spotting or synthesizing probes at known locations on a two-dimensional substrate (Fodor et al. 1991; Schena et al. 1995; Holloway et al. 2002). The significance of our novel approach is that it enables the production of randomly assembled arrays in which the location of a probe is initially unknown (Michael et al. 1998). Random bead loading combined with decoding avoids the need for physical addressing of each element and thus achieves unprecedented levels of miniaturization and very high packing densities by using relatively simple bulk processes (Figs. 1, 2). For example, a typical spotted array with 100-µm center-to-center spacing has ~400-fold lower packing density, and a photolithographically synthesized array (Fodor et al. 1991) with 11-µm center-to-center spacing has about fourfold lower density than that of the arrays described here. The random assembly of 300-nm-diameter beads in 500-nm wells has been reported, a density ~40,000 times higher than that of a typical spotted microarray (Michael et al. 1998).

Although randomly assembled arrays were recognized from the outset as a potentially revolutionary approach to microarray technology, the initial attempts to determine the location and identity of beads could only distinguish a few codes, limiting the usefulness of the approach (Michael et al. 1998). These initial attempts at decoding relied on dye impregnation of beads, but this approach suffered from variability in quantitation, lack of stability, and other problems. A number of other schemes that aim to encode particles directly with combinatorial codes generated by mixtures or spatial arrangements of optical signaling molecules have similar issues (Fulton et al. 1997; Han et al. 2001; Lockhart and Trulson 2001; Nicewarner-Pena et al. 2001; Braeckmans et al. 2002; Chan et al. 2002). We sidestepped the need for complex dye chemistries and painstaking labeling processes by devising a novel, highly efficient decoding algorithm that uses the specificity and reversibility of DNA hybridization.

RESULTS

Design of DNA-Based Decoding

Our algorithm uses sequential hybridizations of dye-labeled oligonucleotides, or decoders, complementary to bead sequences to create a combinatorial decoding scheme for arrays. It is distinct from sequencing by hybridization (SBH), which has been used successfully to characterize sequences de novo by hybridization to all *n*-mers or a well-chosen subset, typically in the range of 4- to 10-mers (Drmanac et al. 1996, 1998; Gunderson et al. 1998; Brenner et al. 2000). Our approach uses longer sequences, each designed to hybridize to a defined target with high specificity. It is capable of decoding, with high accuracy, many 1000s of bead types. Each bead type is defined by a unique DNA sequence that is recognized by a complementary decoder.

To illustrate, we show an example of decoding eight different bead types. We use two fluorescent labels, or states (green and red) in combination with three sequential hybridizations, or

[3]These authors contributed equally to this work.
[4]Corresponding author.
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Article and publication are at http://www.genome.org/cgi/doi/10.1101/gr.2255804. Article published online before print in April 2004.

14:870–877 ©2004 by Cold Spring Harbor Laboratory Press ISSN 1088-9051/04; www.genome.org

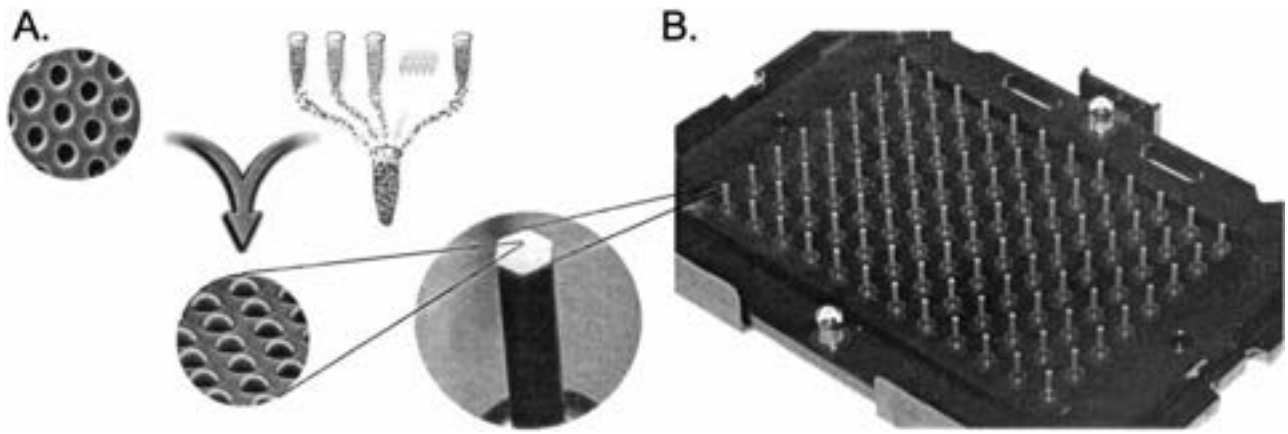


Figure 1 Assembly of a random array. (*A*) Creation of a bead pool and assembly into ~3-µm-diameter wells etched in optical fiber bundles. Once a bead pool is made, it is relatively straightforward to assemble and decode large numbers of arrays. Each array contains ~50,000 beads distributed among 1520 bead types, so that each bead type is represented at ~30-fold redundancy. Scanning electron micrographs are shown of an unassembled and an assembled array containing one bead per well. (*B*) Because individual arrays are only ~1.4 mm in diameter, they can easily be arranged into a 96-array matrix, designed for parallel analysis of samples in standard microtiter plates.

stages. The sequential hybridization process is illustrated for a single bead (bead type 2 of eight) in Figure 2A. In each of the three stages, the bead is "colored" by hybridization to a fluorescently labeled decoder oligonucleotide (Fig. 2A,B). In practice, all beads in the array are labeled simultaneously at each stage, by exposure to a pooled set of decoders, so that the process is intrinsically parallel and efficient.

The combinatorial assignment of green and red within each pool of eight decoders is shown in Figure 2C. There are three decoder pools in total, one for each stage. The stage 1 pool has the first four decoders colored green and the last four colored red. The decoders in subsequent stages are labeled so that after three stages each bead type is assigned a unique three-bit color code. Note that the sequences of the decoders are unchanged from stage to stage; only the fluorescent labels are varied. The bead circled in Figure 2B has the color signature (GRG), or 010 code in binary representation, in which G = 0 and R = 1. Its sequence can be identified as sequence 2 by referring to the color-lookup table in Figure 2C. Although assignment of codes to sequences is unambiguous after three stages, additional stages can be added for error checking purposes (last column of Fig. 2C) to be described below.

In this simple fashion, the eight bead types are decoded with three stages and two color labels. The approach scales exponentially. If there are N bead types and k distinguishable labels, or states, then the number of stages required is $S = \lceil \log_k N \rceil$. Thus, a large number of sequences can be decoded by using only a few labels across a few stages. For instance, four states (colors) combined with eight decoding stages enables up to 65,536 (4^8) different bead types to be decoded.

There are a number of ways of creating different states. Distinct fluorescent labels can be used as described in Figure 2, or the intensity levels of fluorescent labels can be varied to create gray-scale states. We use a process that decodes 1520 different bead types by using three states: two fluorescent "ON" states (FAM and CY3 fluorescent labels) and one nonfluorescent "OFF" state. The logarithmic relationship between the number of bead types and the number of decode stages shows that the 1520 bead types can be decoded in only $\lceil \log_3 1520 \rceil = 7$ stages. In practice, we use an additional stage to enable error checking. Without error checking, a single mistake in resolving a color label in any of the decode stages will lead to misclassification of a bead. This could result from, for example, a weak fluorescent signal or a speck of dust on the array.

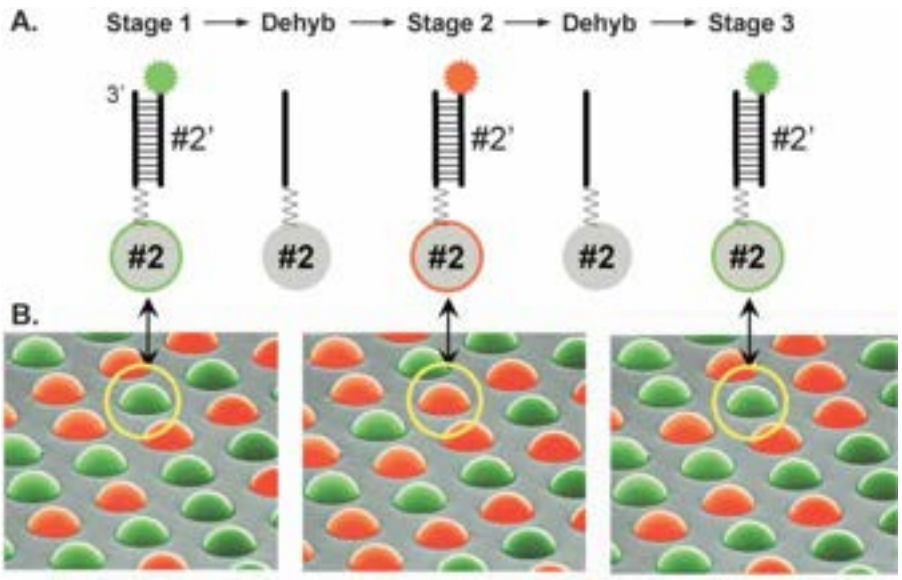
Error Checking

The error-checking concepts that we have developed, and that underlie the robustness of our hybridization-based approach, are based on algorithms from digital information theory (Shannon 1948a,b; Hamming 1986). Although they are well known in other fields, they have not, to our knowledge, previously been applied to microarray manufacture or, indeed, more generally to DNA hybridization. With functional testing of every element of every array, we achieve a level of quality control that is unprecedented in microarray manufacture. As a result, we overcome some of the challenges in quality control that can plague the manufacture of ordered microarrays, which can also suffer from random sources of error (Hubbell and Pevzner 1999; Battaglia et al. 2000; Taylor et al. 2001; Sengupta and Tompa 2002; Shearstone et al. 2002; Hessner et al. 2003).

The simplest form of error checking we have used has a parity bit and is illustrated in Figure 2C. The assigned four-bit codes all have an even parity bit sum and are termed valid codes. An error in a single decode stage is a one-bit error that creates an odd parity, or invalid code. Although the parity-based approach is effective, we have optimized error checking by designing a more advanced scheme that assigns codes in a way that takes into account inherent biases in error rates and enables estimation of the misclassification rate.

In our implementation of three-state decoding, the most common errors are transitions from an ON state, one or two, to the OFF state, zero. Less common are transitions from OFF to ON. Transitions from one ON state to the other ON state are extremely rare. This can be explained by the fact that such transitions require two simultaneous classification errors: a mistaken ON in one color channel and a mistaken OFF call in the other color channel. We used these biases in error rates by designing the decode stages so that every valid code has a fixed number of OFF states. For example, if there are 1520 bead types and we use three-state eight-stage decoding, then each valid code would be designed to be OFF in exactly two stages and ON in exactly six stages (the actual scheme used is a slight variant on this design; see Methods). An example of a valid code would be **21110210**.

With this scheme, it is theoretically impossible to misclassify a code through any number of occurrences of the most common error type: a transition from an ON state to an OFF state. The following events can lead to misclassification: a transition from one ON state to the other, or multiple stage errors with at



C.

		Stage 1	Stage 2	Stage 3	Signature	Code	Parity Code
Sequences	0				GGG	000	0000
	1				GGR	001	0011
	2				GRG	010	0101
	3				GRR	011	0110
	4				RGG	100	1001
	5				RGR	101	1010
	6				RRG	110	1100
	7				RRR	111	1111

Figure 2 Decoding process. (*A*) The sequential hybridization process is illustrated for a single bead, of bead type 2. In stage 1, a complementary decoder hybridizes to the oligonucleotide probe that is attached to the bead (for details of the procedure, see Methods). The decoder is labeled with a fluorophore (green in stage 1, red in stage 2, and green in stage 3). The fluorescent signal is read by imaging the entire array. The array is then dehybridized, and the process is repeated for two more stages. (*B*) A scanning electron micrograph of an array of beads, artificially colored to represent three sequential hybridization stages. The images, taken collectively, reveal a combinatorial code for each bead. Note that the bead circled in yellow has the color signature GRG or code 010. (*C*) Colors, or states, are assigned to individual decoder sequences in each stage to produce a unique combination across stages. This signature, or code, identifies each bead type. As indicated in the parity code column, an extra decoding stage (data not shown) can be performed to provide an error checking parity bit. After three stages of decoding, all the beads are uniquely identified by their color.

least one ON-to-OFF transition and at least one OFF-to-ON transition. Both events are extremely rare. The space of all possible color codes is divided into three categories: used valid, unused valid, and invalid (Table 1). The unused valid codes represent codes that could be assigned to bead types but are not currently in use. Monitoring the number of beads decoding to this category allows an estimation of the true misclassification rate, as described in the Methods section. With little extra cost to the overall process, this error checking scheme monitors the rate of single state errors, minimizes the number of misclassified beads, and permits the number of misclassified beads, one of the key determinants of array quality, to be estimated.

Decoding of Randomly Assembled Arrays

By using this approach, arrays of 1520 different bead types (~50,000 total beads) were decoded 96 at a time in the Sentrix array matrix format. Representative examples from the decoding are shown in Figure 3, and summary statistics are presented in Table 2. Figure 3A shows a set of hybridization images from all eight stages of the decoding process. High signal to noise allows the code of the circled bead to be read by eye. The code is **11012202**, with FAM = 1, Cy3 = 2, and OFF = 0. Furthermore, we can identify this as a valid used code according to the error checking scheme. Figure 3B shows an example of decoding data for a population of beads from a single array imaged in the FAM channel for one out of the eight decode stages. The clear separation between the two modes in the histogram indicates that most beads can be classified unambiguously as OFF or ON. Information of this type is the input for histogram-based or stage-by-stage decoding, which is used for quality control of individual stages. Actual decoding is carried out by using a core-by-core classification algorithm, which makes use of the fluorescence intensity profile of each bead, measured in FAM and Cy3 channels, across all eight decode stages (Fig. 3C) to classify a bead as ON or OFF. In the example of Figure 3C, the code is **02212110**.

By using the core-by-core algorithm, we have decoded many 10s of 1000s of arrays with a median random error rate of $<1 \times 10^{-4}$ per bead (Table 2). The rate was estimated by using the error checking scheme summarized in Table 1. To get a more direct measure of random error rates, we decoded a matrix of 96 arrays twice and considered beads that were decoded to used codes in

Table 1. Distribution and Use of 6561 Codes in the Three-State, Eight-Stage System

Type	Number	Purpose
Used valid codes	1520	Assigned to actual beads.
Unused valid codes	272	Detect rare two-stage errors. Estimate the number of misclassification events.
Invalid codes	4769	Detect single stage errors. Monitor overall decode process; useful for detecting occasional catastrophic failures.

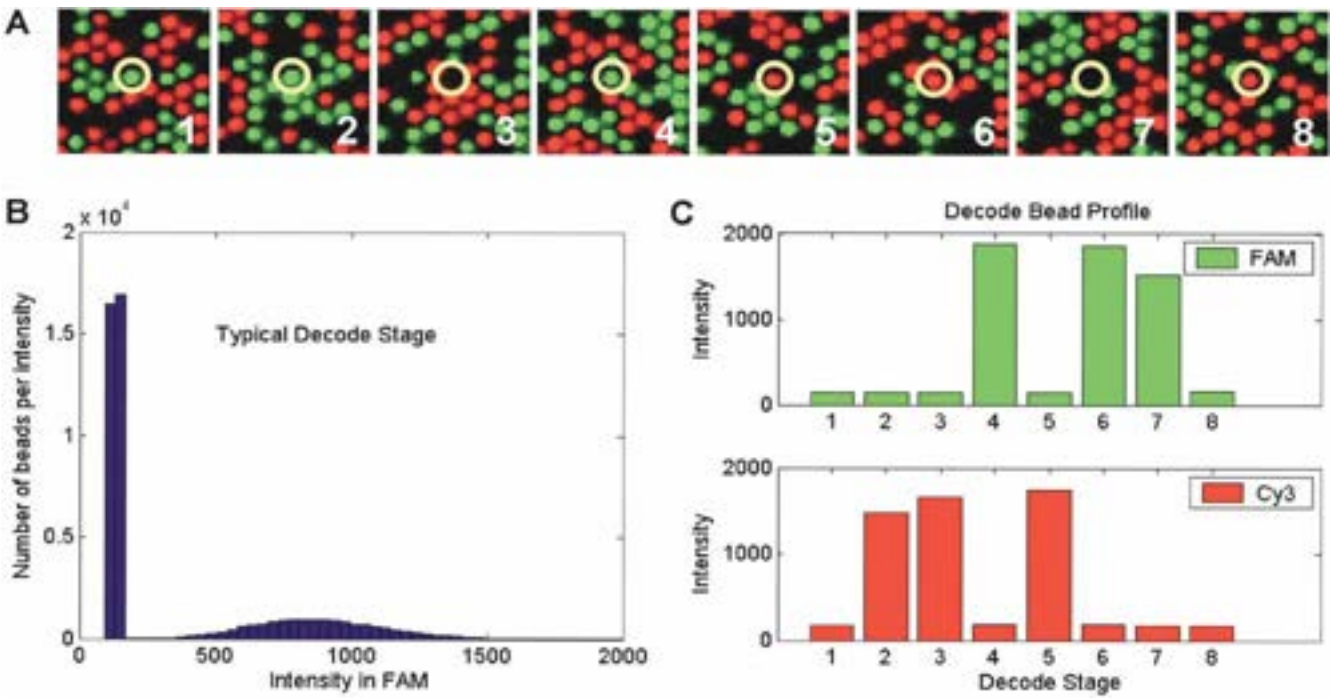


Figure 3 (*A*) Decoding images from eight sequential stages (numbered). Each image is a false-color composite of the FAM and Cy3 grayscale images from each stage. A small region (<0.2%) of a single array is shown. The circled bead is one of up to ~4.8 million in a single 96-array matrix. It has the code **11012202**. A total of 1728 images, each ~5 Mb in size and containing ~1.7 million pixels, are collected in order to decode an array matrix. (*B*) Histogram of bead intensities for a single stage. The low intensity peak includes beads in the OFF state and empty wells. The higher intensity peak includes beads in the ON state. (*C*) The eight-stage intensity profile of a typical individual bead (code = **02212110**) in the FAM and Cy3 channels (~100 counts of intensity are from camera DC offset).

both decoding events (average of 44,912 ± 1098 beads/array). The misclassification rate was then estimated by dividing the number of discrepant calls by the total number of calls. This is an upper bound on the rate, as the errors are distributed among the two decoding events. The mean misclassification rate obtained in this way was 3.8×10^{-5} with a 95% confidence interval of zero to 1.8×10^{-4}. The results are consistent with the estimates obtained in Table 2. This analysis does not account for any systematic misclassification errors, but functional tests (e.g., genotyping comparison studies with other technologies) have not identified any systematic misclassification (data not shown).

Error Rate Impact

The error rate of $<1 \times 10^{-4}$ per bead has a negligible impact on assay accuracy because of the ~30-fold average redundancy and fivefold minimum redundancy of each bead type (Fig. 4). The measured decoding error rate translates to a median of fewer than five misclassified beads per array. Therefore, the chances of more than one random error affecting a given bead type are very low ($\sim 5 \times 10^{-6}$). Given the fact that outlier removal is used in our downstream processes, we estimate that a 100-fold higher average random error rate would have to occur in order to affect our assays (the calculation assumes that the assay is affected if any one bead type on the array has >10% of beads mis-decoded). If we did not use an extra stage for error checking and the number of possible codes was equal to the number of used codes, then any single stage error would lead to misclassification of a bead. Based on the average number of invalid codes generated by our process, we estimate that the average misclassification rate would increase 86-fold. The average array would still perform well, but some fraction of arrays would have unacceptably high misclassification rates.

A fundamental difference between randomly assembled arrays and conventional ordered arrays is that the number of beads (or probes) of each type is intrinsically a random variable with a Poisson sampling distribution for the former (Fig. 4) and is fixed and defined for the latter. Each randomly assembled array is effectively unique, having different numbers and arrangements of beads from array to array yet decoded by a single universal process. This notion is accepted for "liquid arrays" (Fulton et al. 1997), but is fairly radical in the field of spatially fixed microarrays. Nevertheless, the advantage of having multiple beads of each type is that the analytical assay precision is increased by both outlier removal and averaging of replicates (using subsampling of 1 to 20 beads (N) per bead type indicate that the extracted data conform to the theoretical rule of the error of the mean decreasing as $\sqrt{N}$; P. Ng, pers. comm.). At the same time, the random distribution of beads minimizes the chance of any local problem affecting the overall result, increasing robustness of the system. The only added requirement of using "unique" arrays is that the analytical data extraction step must use a uniquely defined template for each particular array. This was easy to implement as part of our data extraction software.

DISCUSSION

Our work provides a high-performance alternative to conventional microarrays. It also expands the reach of microarray assays. For example, we have used a highly miniaturized array format to construct a 96-array matrix for processing many microarray experiments cost-effectively, for ~1500 assays at a time. This provides much needed statistical power that is difficult and prohibitively expensive to obtain by using conventional microarrays, and has the potential to speed the transition of microarray-based assays to large-scale clinical application.

Table 2A. Quality Measures for a Random Sampling of 100 Recently Manufactured Array Matrices, Comprising a Total of 9600 Arrays.

	Average beads in used	Average beads in unused	Average beads in invalid
All arrays	46,576	0.14	153
Array matrix 1	48,653	0.21	202
Array matrix 2	46,872	0.29	106
Array matrix 3	48,500	0.04	70
Array matrix 4	45,367	0.09	90
Array matrix 5	44,898	0.85	252
Array matrix 6	46,549	0.77	172
Array matrix 7	46,480	0.20	106
Array matrix 8	46,596	0.17	88
Array matrix 9	46,837	0.06	84
Array matrix 10	48,260	0.04	89

The first row of the table provides averages over all arrays, and other rows provide data on a subset of 10 randomly chosen array matrices. The results shown are based on raw data, prior to the application of any quality control filters.

Table 2B. Summary Statistics for the 9600 Arrays

	Worst percentile	Mean	Best percentile
Bead types decoded	1520	1520	1520
Decode efficiency	97.6%	99.6%	99.9%
Misclassification rate	1.4×10^{-4}	1.2×10^{-5}	0

Decode efficiency is the number of valid signatures assigned, divided by the total number of beads in the array.

We have used decoded arrays to create new assays for large-scale genotyping (Fan et al. 2003) and gene expression (Yeakley et al. 2002; Fan et al. 2004) using a universal array format. We have also developed gene-specific probe sets for gene expression, and demonstrated limits of detection, precision, and dynamic range that are similar or superior to those obtained with conventional microarrays (M. Chee, K. Kuhn, S. Baker, and T. McDaniel, pers. comm.). Therefore, the technology is versatile and capable of conducting all the types of assays that are currently read out on conventional microarrays. For example, a wide variety of alternative genotyping assays could in principle be implemented on our platform (Gerry et al. 1999; Pastinen et al. 2000; Hardenbol et al. 2003). As a result, this work provides the foundation for a host of important existing applications in genomics, as well as new applications that are under development. Our technology is particularly effective at making large numbers of arrays of a given type, and is complementary to microarray technologies that are useful for screening large amounts of sequence with relatively few arrays (Chee et al. 1996; Patil et al. 2001; Nuwaysir et al. 2002).

Importantly, our technology has been proven in highly demanding and competitive large-scale genomics applications, in particular SNP genotyping (Fan et al. 2003). For example, the majority of the genotyping being carried out for the International HapMap Project, which aims to create a detailed map of common genetic variation across the human genome, is being carried out by using randomly assembled arrays manufactured by our decoding process, in conjunction with a new highly multiplexed genotyping assay that we also developed (Fan et al. 2003). The genotypes we have generated for the HapMap project are publicly available (www.hapmap.org). We routinely achieve a combination of call rates of >99.9% together with accuracy of 99.7% to 99.9%, with a capacity to process over a million genotypes per day that is scalable to much higher levels (Fan et al. 2003).

Random arrays have been particularly useful for the accurate, high-throughput, and cost-effective analysis of large numbers of samples for ~1500 assays at a time, a need that was not met by conventional arrays. However, if random arrays are to realize their full potential, the capacity of the decoding scheme must be increased to allow the analysis of 10s or 100s of 1000s of assays per sample. Our approach to decoding is flexible and scalable. We have used a single decode sequence per bead, which works well for decoding 1000s of bead types. The decoding of 100,000s of bead types by the current process would require the synthesis of 100,000s of fluorescently labeled decoder oligos—an expensive and time consuming task. This bottleneck can be overcome by using multiple decoding sequences on each bead type such that if pairs of sequences are used, up to 10^6 (1000×1000) unique combinatoric sequences can be formed from just 2000 primary decoder sequences. By using this combinatoric approach, the decoder pools would only contain a complexity of 1000 to 2000 different sequences rather than 10^6 sequences.

Finally, the decoding algorithm is general and can, in principle, be applied to any spatially fixed collection of objects or molecules that are associated with specific DNA sequences. In genomics, the classification and characterization of large collections of sequences is often a key step in the analysis of complex biological systems. For example, a library of DNA clones is traditionally searched for a single gene of interest by hybridization to a labeled DNA probe (Sambrook 1989). The approach described here would allow a search for 1000s of genes at a time, while distinguishing closely related members of gene families and perhaps alternative splice forms. Similarly, electrophoretic separations of complex mixtures of nucleic acids are often probed to characterize a gene or its mRNA (Southern 1975; Alwine et al. 1979; Liang and Pardee 1992); this can also be parallelized. Fi-

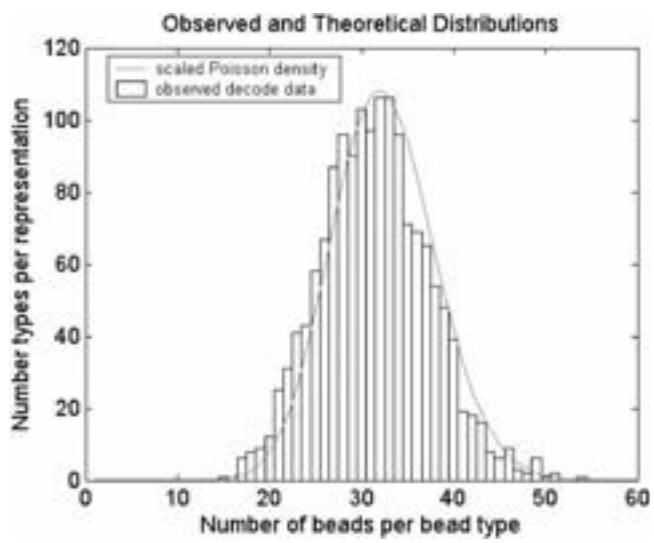


Figure 4 Bead representation histogram from a representative decoded array overlaid with a scaled Poisson density function. The loading of each array is a sampling of beads from a near infinite bead pool. Almost $N \sim 50{,}000$ beads are sampled, and the probability, p, that a sampled bead belongs to a particular type is approximately one divided by the number of bead types. Because N is large, p is small, and the initial bead pool is near infinite, the number of beads from each bead type is well modeled by a Poisson distribution with mean N_p. With 1520 bead types, we average >30 replicate beads per bead type, and the probability that any bead type has fewer than five replicate beads is extremely low ($\sim 5.5 \times 10^{-6}$).

nally, fluorescence in situ hybridization (FISH), a powerful class of methods with many applications, could be applied to 1000s of genes simultaneously. To illustrate, FISH with combinatorially labeled oligonucleotide probes has been used to measure transcription from 10 genes in a single cell (Levsky et al. 2002). The decoding strategy we describe could potentially allow transcription to be measured for all genes in a single cell.

In conclusion, we have developed a new and scalable way to make a novel type of microarray. The highly miniaturized arrays have performed well in a variety of applications. The decoding approach used to make them is both accurate and robust and can, in principle, be used to identify not only DNA sequences on beads but also other collections of DNA sequences.

METHODS

Preparation of Oligonucleotide-Linked Beads and Bead Pools

A set of 1536 universal capture oligonucleotide sequences was synthesized. Each sequence was individually immobilized on activated beads, as follows, to create 1536 bead types. Silica beads ~3 µm in diameter (Bangs Laboratories, Inc.) were amino functionalized by incubation in 2.5% 3-amino-propyl-trimethoxysilane (Aldrich) in ethanol for 1 h at RT and then activated by reaction with 2% 2,4,6-trichloro-1,3,5-triazine (Aldrich) in acetonitrile for 2 h at room temperature. Synthetic oligonucleotides labeled at the 5′ terminus with a primary amine were covalently attached to the activated beads by overnight reaction at 50°C in a solution of 3 M NaCl and 100 mM sodium carbonate (pH 11). All reagents were of highest purity grade. Empirical measurements indicated that, on average, each bead carried on the order of 10^6 oligonucleotides. Following quality assessment, 16 of the bead types were discarded due to low signal-to-noise ratios. The remaining bead types were combined to create a pool containing 1520 functional bead types, each representing a unique capture sequence. The sequences were designed to serve as non-interacting decodable address sequences in addition to their function as probes that capture assay products from solution. They were selected to be 22 to 24 bases long with minimal cross-complementarity, similar GC content and Tm, no runs of a single base longer than five, and low similarity to human genomic sequences.

Preparation of Oligonucleotides and Pools Used in the Decode Process

Three sets of 1520 oligonucleotides complementary to the bead sequences were synthesized (Illumina Oligator synthesis). One set was unlabeled (corresponding to the OFF state), another with FAM, and a third with Cy3. The dye labels were incorporated during oligonucleotide synthesis by using 5′ phosphoramidites (Trilink Biotechnologies). After synthesis and deprotection, each oligonucleotide type was individually purified by using 96-well reverse-phase cartridge purification to yield labeled products >75% in purity. These sets of oligonucleotides were used to create eight unique decode pools, according to the strategy described below. Each pool contained 1520 decode sequences, each at a concentration of 10 nM.

Design of Decoder Pools

The strategy for the design of decoder pools to enable error checking, described in the main text, included the condition that all valid codes have exactly two OFF states, which allows for a maximum of 1792 codes. To enable the decoding of more bead types, we pooled the decoders so that valid codes have either exactly two OFF states or exactly five OFF states. The transition events that lead to misclassification are the same as described above, except that errors of the type (ON to OFF) or (OFF to ON) occurring in three different stages could also lead to a misclassification event. Three errors from ON to OFF could occur if a bead falls out of the array in the middle of decoding. To eliminate this source of error, all codes ending in three or more OFF states were removed from the set of valid codes. Finally, we eliminated any codes that do not have at least one ON state in each of the color channels that we use. The fact that each bead must show specific signal in two color channels during the decode process provides an additional quality check. The total number of valid color codes in this scheme is 2012.

Assembly of Array Matrices

Array matrices were manufactured in the following way: 96 optical fiber bundles were set in a rigid frame, in an 8 × 12 matrix that matches the layout of a standard 96-well microtiter plate. Each ~1.4-mm-diameter hexagonally packed bundle contains 49,777 individual glass optical fibers fused together into a monolithic unit. The bundles were polished at both ends to a tolerance of ~1 µm planarity across the entire matrix. One end served as the imaging surface and was used for the collection of fluorescence intensity data. The opposite end was etched in weak acid to create a well ~3 µm in diameter at the end of each optical fiber. The fiber bundles were loaded by pipetting ~0.4 µL (0.12 mg) beads in ethanol onto the end of each bundle, allowing the ethanol to evaporate, and removing excess beads. The assembled arrays were quite stable. Following eight stages of decoding and an overnight analytical hybridization (high salt at 48°C to 55°C), bead retention was typically >97%.

Decoding

Following bead assembly, arrays were hybridized to pools of 1520 decoders, each at 10 nM in decode buffer (600 mM NaCl, 60 mM potassium phosphate, 0.06% Tween-20, and 40% formamide at pH 7.6), for 12 min at room temperature. Following hybridization, three 1-min washes in wash buffer (167 mM NaCl, 16.7 mM potassium phosphate, 0.017% Tween-20 at pH 7.6) were used to remove unbound oligonucleotides. The arrays were then imaged at 1.0-µm resolution by using a 12-bit, 2000 × 3000-pixel CCD camera (Quantix 36E, Roper Scientific) and a standard achromatic 0.3 NA microscope imaging objective (field of view [FOV] = 2 mm) in a custom-engineered high-throughput imaging system (Barker et al. 2003). The imaging system uses an X, Y, Z stage assembly and positioning and autofocus software to collect images from all 96 arrays of a Sentrix array matrix automatically. Fluorescence excitation was performed by using a 300-W xenon arc lamp (ILC technology) and appropriate emission/dichroic/excitation filter sets. The FAM and Cy3 color channels were imaged separately. The light intensity at the sample was ~20 to 35 mW. This imaging design minimizes spectral cross-talk between dyes because excitation and emission are done on peak. After imaging, the arrays were dehybridized by dipping into 0.1 N NaOH for 1 min and were then neutralized in decode buffer. The process of hybridization, washing, image collection, and dehybridization was carried out until eight hybridization stages were completed. The arrays were washed in water and ethanol, dried in nitrogen, and sealed with desiccant in a foil package.

Image Processing and Data Extraction

A core corresponds to an etched well in the optical fiber bundle and has a high probability of containing a bead. We developed algorithms and custom image processing software to discover the locations of cores in decode images and extract intensity data from them (Galinsky 2003a,b). The software identified, aligned, and indexed the cores in a process termed registration. The shift, rotation, and scale of each image were determined relative to a template image as part of this process. After registration, the core indices and locations were matched across the set of decode images. Intensity information for each core was then obtained by averaging a three-by-three-pixel region centered on the core. The diameter of each core is approximately three microns, and each pixel is a one micron square. Many 1000s of decoding images are collected in a day in the production facility. Thus, an automated image analysis pipeline was created to facilitate high-throughput processing.

Decoding Algorithms

We describe two algorithms used to assign decode signatures to beads. The first is called stage-by-stage decoding. In this approach, an intensity histogram is computed for each color channel of each decode stage. The histogram is bimodal because each stage and color channel will have beads that are in the ON state and beads that are in the OFF state. An intensity value that separates the ON state from the OFF state is chosen, and all cores are assigned a zero or one, depending on whether their intensity value is less than or greater than the separation threshold. The values assigned for each stage and color channel are combined into the decode signature. This algorithm is highly effective when the OFF state population is well separated from the ON state population. Further, the method is insensitive to shifts caused by stage-to-stage variability in intensity.

Pseudocode for Stage–by–Stage Decoding

For each stage do
For each color channel do

1. *Input the N core intensity values.*
2. *Compute intensity histogram using 100 bins.*
3. *Locate the bin with the maximum height peak within the first 25 bins, and the bin with the maximum height peak within the last 75 bins.*
4. *Find the bin with the minimum height peak between the two maxima.*
5. *Determine C, the median intensity of the minimum height peak.*
6. *Label all cores with intensity lower than C with zero, and all cores with intensity greater than C as one.*

Tabulate the zero and one stage and color information into the decode signatures.

The second algorithm is called core-by-core decoding. For each bead and color channel, we consider the eight intensity values across decode stages. The values are sorted, and the greatest relative intensity increase is determined. This is the separation between the ON and OFF states for the core. The same procedure is repeated for all beads in both color channels. The results are combined to give the decode signatures.

Pseudocode for Core–by–Core Decoding

For each core do
For each color channel do

1. *Input the m intensity values for the core and color channel across stages.*
2. *Let $I_1 \ldots I_m$ be the sorted intensity values.*
3. *Let $J_k = (I_{k+1} - I_k)/I_k$, $k = 1 \ldots m - 1$ be the relative intensity jump from stage k to stage k + 1.*
4. *If the greatest relative jump occurs between stage K and K + 1, then assign zero to the core in stages 1 … K, and assign one to the core in stages K + 1 … m.*

Tabulate the zero and one core and color information into the decode signatures.

The two methods give virtually identical results. In practice, we use the core-by-core method to decode the arrays, and obtain quality control information from the histograms. As part of the decoding process, quantitative metrics for array quality are output automatically and can be stored in a database. All processing and quality metric generation takes ~20 min on a standard personal computer for a matrix of 96 arrays.

Estimation of Misclassification Rate

There are 1792 eight-stage color codes that have exactly two OFF states. A subset of these codes, (e.g., 1520) can be randomly selected and used in the design of decoder pools. The remaining 272 codes are unused. If a bead is misclassified (identified as the wrong bead type), the error cannot be observed because the number of beads of each type is random. However, because the used and unused color codes have the same form and are partitioned randomly, the number of beads that decode to unused color codes can be used to estimate the random misclassification rate. The estimate is given by $[B_{unused}/(B_{used} + B_{unused})] \times [(C_{used} - 1)/C_{unused}]$, where B_i is the number of beads decoding to category i and C_i is the total number of color codes in category i. In other words, the estimate is the relative number of beads decoding to unused codes scaled by the ratio of the number of codes in the used and unused categories. In the current example, $C_{used} = 1520$ and $C_{unused} = 272$, but the computation is analogous for any other decode space design.

ACKNOWLEDGMENTS

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WEB SITE REFERENCES

www.hapmap.org; International HapMap Project.

Received December 8, 2003; accepted in revised form January 29, 2004.

Subject Re: Confidential: 1536 beads, but only use 1520 zip codes

From Monib Zirvi <matzirvi@yahoo.com>

To: Francis Barany <barany@med.cornell.edu>

Cc: Pearson, Matthew <mpearson@AKINGUMP.com>, Valerie Cross <vlc1@cornell.edu>

Date Nov 5, 2015 at 1:10 PM

It is very suspicious that the 16 were discarded and that there were exactly 16 zipcodes submitted in their patent application. Way too many coincidences...

Sincerely,

Monib Zirvi

Sent from my iPhone

On Nov 5, 2015, at 1:02 PM, Francis Barany <barany@med.cornell.edu> wrote:

Dear Matthew,

Thanks again for your patience this morning. I apologize again that we came across as upset — we are not upset with you — just that we are very passionate about our work.

I did go back and found the paper by Gunderson et-al 2004 (enclosed). By that point they were already using zip-codes in the size range of 22-24 (perhaps someone told them to “mix in some 22-mers and 23-mers with the 24-mers, to get around Barany’s patents”), but it doesn’t matter, as the 22-mers most-likely differed from each other and other sequences by 6 or more bases (based on probability alone).

They claim to synthesize 1536 beads, with 16 of the bead types discarded due to low signal-to-noise ratios. It would be interesting to understand why these 16 failed, was there anything wrong with their sequence design, their synthesis, real Tm lower

sequence design, their synthesis, real Tm lower than calculated Tm — or were they discarded for "another" reason?

Again, please let us know how we can be of further assistance.

All the best,

Francis

[redacted]

METHODS

Preparation of Oligonucleotide-Linked Beads and Bead Pools

A set of 1536 universal capture oligonucleotide sequences was synthesized. Each sequence was individually immobilized on activated beads, as follows, to create 1536 bead types. Silica beads ~3 μm in diameter (Bangs Laboratories, Inc.) were amino functionalized by incubation in 2.5% 3-amino-propyl-trimethoxysilane (Aldrich) in ethanol for 1 h at RT and then activated by reaction with 2% 2,4,6-trichloro-1,3,5-triazine (Aldrich) in acetonitrile for 2 h at room temperature. Synthetic oligonucleotides labeled at the 5 terminus with a primary amine were covalently attached to the activated beads by overnight reaction at 50°C in a solution of 3 M NaCl and 100 mM sodium carbonate (pH 11). All reagents were of highest purity grade. Empirical measurements indicated that, on average, each bead carried on the order of 106 oligonucleotides. Following quality assessment, 16 of the bead types were discarded due to low signal-to-noise ratios. The remaining bead types were combined to create a pool

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They were selected to be 22 to 24 bases long with minimal
crosscomplementarity,
similar GC content and Tm, no runs of a single
base longer than five, and low similarity to human genomic
sequences.

View less

<Decoding_random_Zipcode_arrays_Gunderson_Illumina_2004.pdf>

Subject CONFIDENTIAL AND PRIVILEGED
RE: Walt stuff / Colored beads /
Questions-comments to Matthew

From Francis Barany
<barany@med.cornell.edu>

To: Pearson, Matthew
<mpearson@AKINGUMP.com>,
Valerie Cross <vlc1@cornell.edu>

Cc: Monib Zirvi <matzirvi@yahoo.com>,
Francis Barany
<barany@med.cornell.edu>

Date Feb 24, 2016 at 5:00 PM

Dear Matthew and Valerie,

Matthew, thank you again for a terrific job on Monday. I am very happy that you and Diane are representing us.

Monib had some thoughts below, which I am passing on to you...

With regards to the case:

1. See enclosed David Walt's interview articles and "revisionist history". In next email I am sending you his papers, including a review he wrote. How do we counter this?

2. The pegs in holes is a great analogy for us. Monib food a company that makes wooden ones (below), and the "Lite Brite" pegs, which are immobilized by attaching different solid supports together (non-unitary). I ordered 2 sets of Lite Brite pegs for you (as well as batteries), being shipped to Akins Gump from Amazon:
Order #002-4775596-6654620. I will send you the email confirmation, kindly let me know when you get it.

3. Monib specifically remembers making mounds of

polyacrylamide gels on glass slides, specifically small mounds to attach oligonucleotides to the mounds. The mounds were sitting on glass. He

mounds. The mounds were sitting on glass. He remembers going to Minnesota to the micro-fab lab to etch wells in silicon, to fill with polyacrylamide. ABI also made wells for us in Silicon and sent them to us in 1996. We did a major lab cleanup on Tuesday, and FOUND those Silicon wafers with holes. Photo and letter enclosed.

4. How do we respond in court when the other side makes comments that are condescending, sarcastic, disparaging, and untrue? I often have difficulty in distinguishing when someone is being sarcastic to me…

5. When Rip left, I said goodbye to him and mentioned "Matthew is doing a great job, don't you think?", to which he responded: "Considering what he has to work with." Given my difficulty in interpreting nuances, perhaps you can explain what that was about…

6. ABI just bought Affymetrix, the direct competitor to Illumina. As you know, there is a history here. Will you be able to get access to that history?

With regards to the IPR:

Have done considerable homework here and found a number of "issues" that I believe will be of interest.

1. Would you provide some potential times for next week for a webex meeting? We are already a month behind due to the Markman hearing. There is no question they timed it this way.

2. Is there anything in particular you would like me to look at prior to then?

Thanks a million for all your support. With best wishes,

Francis

[redacted]

[redacted]

BioArray Q&A Tufts' David Walt on the …

ATT00001.htm

esselen_address_walt_award_04_18_2…

ATT00002.htm

Visionary David Walt_Tufts Tech Transf…

ATT00003.htm

ATT00004.htm

Silicon Chips with Wells_Letter_Aug_1_…

ATT00005.htm

Subject CONFIDENTIAL AND PRIVILEGED
RE: Walt Papers

From Francis Barany
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To: Pearson, Matthew
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Date Feb 24, 2016 at 5:01 PM

FYI.

Francis

[redacted]

A fiber-optic DNA biosensor microarray …

ATT00001.htm

Bead-based Fiber-Optic Arrays_Walt_S…

ATT00002.htm

Fiberoptic DNA Sensor Array Capable o…

ATT00003.htm

High-density fiber-optic DNA random mi…

ATT00004.htm

Randomly Ordered Addressable High-D…

ATT00005.htm

Screening unlabeled DNA targets with r…

ATT00006.htm

Very_High_Density_Sensing_Arrays_R…

ATT00007.htm

Subject Re: CONFIDENTIAL AND PRIVILEGED RE: Walt stuff / Colored beads / Questions-comments to Matthew

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To: Francis Barany <barany@med.cornell.edu>

Cc: Pearson, Matthew <mpearson@AKINGUMP.com>, Valerie Cross <vlc1@cornell.edu>

Date Feb 24, 2016 at 5:22 PM

I'm so happy you found the silicon etched with wells.
I had mentioned wells and other configurations that were
Used in my deposition. They conveniently omitted
All of that during the Markman hearing.

Monib

Sent from my iPhone

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<barany@med.cornell.edu> wrote:

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<BioArray Q&A Tufts' David Walt on the Evolution of Optical Sensor Arrays_GenomeWeb_09_08_2009.pdf>
<esselen_address_walt_award_04_18_2014.pdf>
<Visionary David Walt_Tufts Tech Transfer.pdf>

<Wells in Silicon_1996_v1.JPG>
<Silicon Chips with Wells_Letter_Aug_1_1996.pdf>

> Begin forwarded message:
>
> **From:** Monib Zirvi <matzirvi@yahoo.com>
> **Subject: Re: Confidential & Private: Walt stuff / Colored beads / 5 questions-comments to Matthew**
> **Date:** February 23, 2016 at 10:33:19 PM EST
> **To:** Francis Barany <barany@med.cornell.edu>
> **Reply-To:** Monib Zirvi <matzirvi@yahoo.com>
>
> Dear Francis,
>
> Just wanted to summarize some points we discussed on the drive back yesterday.
>
> 1. David Walt, interview articles and revisionist history.
>
> 2. Lite Brite pegs are immobilized by attaching different solid supports together (non-unitary).
>
> > Pegs and Lite Brite

http://www.officeplayground.com/mobile/Peg-Game-P1691.aspx?gclid=CIzA_sbyjMsCFYwfhgodfIIAYg

Lite Brite

http://www.hasbro.com/en-us/search?q=Lite+Brite

Square ones fro Walmart:

http://www.walmart.com/ip/39080579?wmlspartner=wlpa&adid=22222222228027317485&wl0=&wl1=g&wl2=m&wl3=43910681672&wl4=&wl5=pla&wl6=84286167632&veh=sem

Patent talks about lite brite pegs being made my attaching different

components together. Pegs are also immobilized by inserting into a hole.

Wooden Triangle Peg Game

image

Wooden Triangle Peg Game

Shop for Cool Office Toys, Office Games, Desktop Toys and accessories that help make work more fun. Get the best deals here at Office Playground!

View on www.officeplayground... Preview by Yahoo

3. I specifically remember making mounds of polyacrylamide gels on glass slides with Herman Blok, specifically small mounds to attach oligonucleotides to the mounds. The mounds were sitting on glass (adsorbed). I also remember visiting the Microfabrication facility at the University Minnesota etch wells in silicon, to fill with polyacrylamide.

4. How do we respond in court when the other side makes comments that are condescending, sarcastic, disparaging, and untrue?

5. How do we correct the “revisionist history” about the invention of zip-codes?

6. On the microsatellite repeat work, the deliberate gap and deliberate exclusion of the prior polymerase extension step was a purposefully designed experiment to measure lengths of the mononucleotide and dinucleotide repeat. Also, for ALL templates (natural and artificial), an extension step done by a polymerase would obviously create adjacent primers after which only a ligase in a ligase detection reaction could produce the full product to detect. Those extended primers would have to be adjacent and abut each other for the ligase to ligate them. This is a ligase detection reaction. Even if a polymerase inserts a base, we prove that with the single gap and not having adjacent and abutted input primers to a ligase detection reaction, the ligase would be the one detecting, not the polymerase. I clearly explained that to them in my deposition. So they are being sneaky by showing selective isolated snippets out of context from the depositions.

7. As I mentioned, I found this interesting statement regarding encoding beads with DNA from David Walt:

> https://www.genomeweb.com/arrays/bioarray-qa-tufts-david-walt-evolution-optical-sensor-arrays

8. One final point.

All organizations behave in line with what their leadership demonstrates and tolerates:

1. John Zebala shared priviledged information and Illumina later went on

and used that information after they terminated the relationship.

2. David Walt saw priviledged information after signing agreements. Then stopped the relationship and went on to use the information.

3. Illumina signed documents and was given priviledged information with ABI and then went on again to do the same.

Sincerely,

Monib Zirvi

Subject Re: CONFIDENTIAL AND PRIVILEGED RE: Walt Papers

From Monib Zirvi <matzirvi@yahoo.com>

To: Francis Barany <barany@med.cornell.edu>

Cc: Pearson, Matthew <mpearson@AKINGUMP.com>, Valerie Cross <vlc1@cornell.edu>

Date Feb 27, 2016 at 11:11 AM

Dear All,

Note the use of the words "Universal" and "addressable" in this review article.

Fluorescence-based fibre optic arrays: a universal platform for sensing.

Review article

Epstein JR, et al. Chem Soc Rev. 2003.

Authors

Epstein JR[1], Walt DR.

Author information

[1]Max Tishler Laboratory for Organic Chemistry, Department of Chemistry, Tufts University, Medford, Massachusetts 02155, USA.

Citation

Chem Soc Rev. 2003 Jul;32(4):203-14.

Abstract

Optical fibres provide a universal sensing platform as they are easily integrated with a multitude of different sensing schemes. Such schemes enable the preparation of a multitude of sensors from

relatively straightforward pH sensors, to more complex ones, including artificial olfaction sensors, high-density oligonucleotide arrays, and high-throughput cell-based arrays. Imaging fibre bundles comprised of thousands of fused optical fibres are the basis for an optically connected, individually addressable parallel sensing platform. Fibre optic imaging bundles possess miniature feature sizes (3-10 micron diameter fibres), allowing high-density sensor packing (approximately 2 x 10(7) sensors per cm2). Imaging fibre bundles transmit coherent images enabling combined imaging and sensing, relating the responses monitored by the sensor to observable physical changes. The individual fibre cores can also be selectively etched to form a high-density microwell array capable of housing complementary sized microsensors. The miniature feature sizes facilitate a faster response and more sensitive measurement capabilities. The platform is extremely versatile in its sensing design, allowing the sensing scheme to be tailored to fit the experimental design, whether for monitoring single analytes or more complex multiplexed assays. A number of sensing schemes and applications are described in this review.

PMID 12875026 [PubMed - indexed for MEDLINE]

Sent from my iPhone

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> FYI.
>
> Francis
>
> [redacted]
>
> [redacted]

<A fiber-optic DNA biosensor microarray for the analysis of gene expression_Walt_1996 copy.pdf>
<Bead-based Fiber-Optic Arrays_Walt_Science_2000 copy.pdf>
<Fiberoptic DNA Sensor Array Capable of Detecting Point Mutations_Walt_1997 copy.pdf>
<High-density fiber-optic DNA random microsphere array_Walt_2000 copy.pdf>
<Randomly Ordered Addressable High-Density Optical Sensor Arrays_Walt_1998 copy.pdf>
<Screening unlabeled DNA targets with randomly ordered fiber-optic gene arrays_Walt_2000 copy.pdf>
<Very_High_Density_Sensing_Arrays_Review_Walt_2008.pdf>

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View less

Subject Relevant paper

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Here is a very relevant paper which cites Barany and Gerry as clear origin of universal microarray and ligase detection.

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http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2648982/pdf/1471-2180-8-237.pdf

Sent from my iPhone

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Date Feb 27, 2016 at 12:19 PM

Dear Monib, George, and Bob,

Monib, thank you for finding this - excellent.

The reason I had not sent this paper to Matthew and Valerie previously is that I am not able to access it through PubMed — i.e. it is not available at Weill Cornell Medicine Library.

George and Bob — would you be able to access this through your Chemistry department or personal subscription to ACS? (Valerie: ACS = American Chemical Society — not Cancer).

Whoever gets it first, please email to all.

Most appreciated!

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To: Francis Barany <barany@med.cornell.edu>

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Date Feb 27, 2016 at 12:50 PM

When we made fluorescent Arrays, detection was with
CCD camera-based fluorescent scanner. Using this fiberoptic CCD camera is not an advance in the array component or multiplex ligation component. This should be emphasized.

http://www.maxtool.com/video-snake-swj-3188d-pipe-wall-inspection-system-65-complete-color-camera-system-scratch-dent?google=1&CAWELAID=230005740000038512&CAGPSPN=pla&gclid=CKPtqsy9mMsCFYsAaQodGiIAVA
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Date Feb 27, 2016 at 3:15 PM

see attached

please confirm that's what you want

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PMID 12875026 [PubMed - indexed for MEDLINE]

Sent from my iPhone

View less

--
George Barany
Distinguished McKnight University Professor of

Chemistry
University of Minnesota
Department of Chemistry
[redacted]

b300617d.pdf

View Article Online / Journal Homepage / Table of Contents for this issue

Fluorescence-based fibre optic arrays: a universal platform for sensing

Jason R. Epstein and David R. Walt*

The Max Tishler Laboratory for Organic Chemistry, Department of Chemistry, Tufts University, Medford, Massachusetts 02155

Received 15th January 2003
First published as an Advance Article on the web 14th April 2003

Published on 14 April 2003. Downloaded by University of Minnesota - Twin Cities on 27/02/2016 20:10:17.

Optical fibres provide a universal sensing platform as they are easily integrated with a multitude of different sensing schemes. Such schemes enable the preparation of a multitude of sensors from relatively straightforward pH sensors, to more complex ones, including artificial olfaction sensors, high-density oligonucleotide arrays, and high-throughput cell-based arrays. Imaging fibre bundles comprised of thousands of fused optical fibres are the basis for an optically connected, individually addressable parallel sensing platform. Fibre optic imaging bundles possess miniature feature sizes (3–10 micron diameter fibres), allowing high-density sensor packing ($\sim 2 \times 10^7$ sensors per cm^2). Imaging fibre bundles transmit coherent images enabling combined imaging and sensing, relating the responses monitored by the sensor to observable physical changes. The individual fibre cores can also be selectively etched to form a high-density microwell array capable of housing complementary sized microsensors. The miniature feature sizes facilitate a faster response and more sensitive measurement capabilities. The platform is extremely versatile in its sensing design, allowing the sensing scheme to be tailored to fit the experimental design, whether for monitoring single analytes or more complex multiplexed assays. A number of sensing schemes and applications are described in this review.

1 Optical fibres

Optical fibres consist of a glass or plastic core surrounded by a clad material of lower refractive index. Based on the difference in refractive indices, light is reflected at the core-clad interface (Figure 1). Light propagates through the fibre core and is

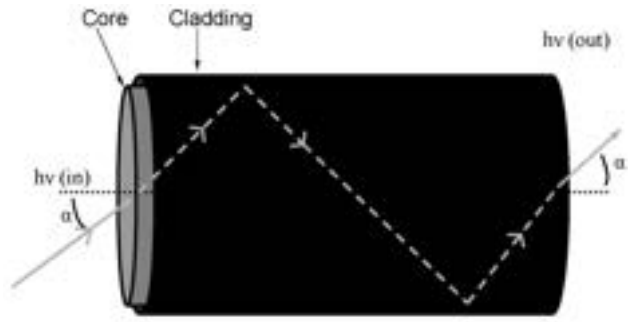

Fig. 1 Schematic of an optical fibre. Light propagates in the fibre along the entire length due to the refractive index differences of the core and clad materials.

transmitted the length of the fibre with minimal attenuation. As such, optical fibres are an ideal platform for sensing as they enable light to be carried over long distances. Conveying a

Jason R. Epstein received his Bachelor's degree from Siena College in 1992 and his Master's degree from Portland State University in 1999. From 1992–97, Jason was employed at Cambridge Isotope Laboratories as a process chemist. He is currently working towards his PhD in chemistry/biotechnology in the laboratory of David Walt at Tufts University. His main research focus concerns practical applications for fiber optic microsphere-based oligonucleotide microarrays.

Jason R. Epstein

David R. Walt is Robinson Professor of Chemistry at Tufts University. He received a BS in Chemistry from the University of Michigan and a PhD in Chemical Biology from SUNY at Stony Brook. After postdoctoral studies at MIT, he joined the chemistry faculty at Tufts. Professor Walt served as Chemistry Department Chairman from 1989 to 1996. Dr Walt serves on many government advisory panels and boards. He is Executive Editor of Applied Biochemistry and Biotechnology and serves on the editorial advisory board for numerous journals. Dr Walt is the Scientific Founder of Illumina, Inc. He has received numerous national and international awards and honors recognizing his work and is a fellow of the American Association for the Advancement of Science. His research interests are in the fields of sensors, biosensors, micro and nano-arrays, artificial olfaction, and functional screening.

David R. Walt

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signal over long distances allows optical fibres to be used in remote or hazardous sensing applications that typically cannot be addressed with other analytical techniques. Fluorescence-based methods are particularly amenable to fibre optic platforms. For fluorescence-based sensing, excitation light is delivered through the fibre to a fluorescent indicator attached to the fibre's distal end, and the resulting isotropic fluorescence emission is transmitted back through the fibre to a detector. Fluorescence-based sensing techniques are versatile, enabling interrogation of multiple optical properties simultaneously, including excitation and/or emission wavelengths, emission intensity, and fluorescence lifetime. Fluorescence assays can be readily multiplexed by simultaneously using multiple indicators reporting at different wavelengths. Multiplexed fluorescence-based fibre optic sensors have been applied to the detection of ions and organic compounds, as well as numerous biological compounds.[1,2]

The desire for parallel interrogation and high throughput analysis has prompted the development of sensor array platforms. Imaging fibre bundles are already formatted into an array, composed of thousands of single core fibres coherently fused, with each fibre in the bundle maintaining its own independent light pathway (Figure 2). A fibre bundle with 3.0

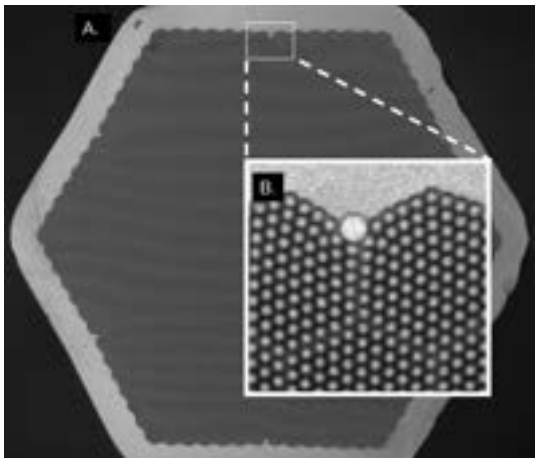

Fig. 2 An image of a 1 mm^2 fiber bundle containing ~50,000 total 3 micron individual fibres. A) An entire hexagonally packed bundle. B) A higher magnification of the fiber bundle showing the miniature feature sizes and close-packed arrangement. The large circle is a positional marker built into the array.

μm diameter cores and an overall 1 mm bundle diameter contains over 50,000 individual fibres. More flexible bundles with smaller diameters and smaller numbers of total fibres are also available. The small dimensions and close packing arrangement associated with optical fibre bundles account for their use as high-density sensor arrays. Imaging fibres are aptly suited for use as sensor arrays, enabling rapid, simultaneous analysis of complex mixtures.

2 Optical fibre-based sensors

The work described in this review employs fluorescence as the signal transduction method for optical fibre-based sensing. This review highlights the advantages of the fibre optic platform for fluorescence-based sensing, including their miniature sensor size, high sensitivity, high throughput, and versatility. The next two sections describe both the general instrumentation and common sensor fabrication methods, including the various approaches for attaching the requisite sensing chemistry to optical fibres. Subsequent sections describe optical fibre-based sensor applications. While the fibre optic platform described in this review employs imaging bundles as the substrate, the fundamental sensing chemistries were initially developed for single core fibre optic sensors and therefore, they will be mentioned briefly in several sections.

2.1 Fluorescence imaging systems

Although each type of fibre optic sensor requires specific instrumentation, there are some common system components for all fluorescence-based sensing systems (Figure 3). An

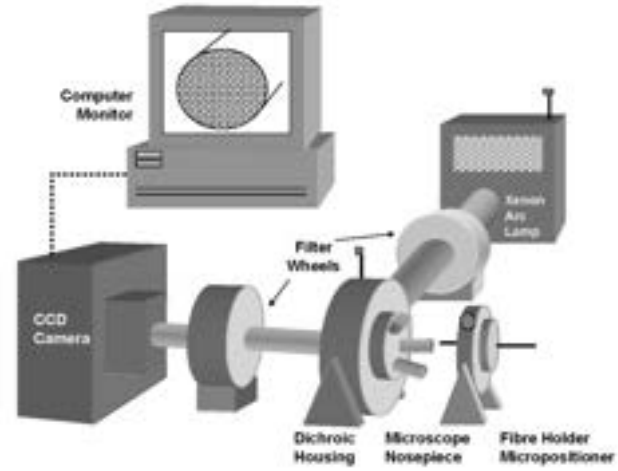

Fig. 3 The general setup of the custom-built imaging systems consisting of a computer-controlled modified epifluorescence microscope.

excitation light source, such as a laser, light emitting diode, or white light source, is used to excite the fluorescent indicator. In many research applications, a white light source, such as a xenon arc lamp, is filtered through an excitation filter to provide monochromatic light. A white light source is extremely flexible, as it can excite fluorophores over the entire visible spectrum, which enables an extensive range of fluorescent dyes to be used. Excitation light entering the fibre is collimated and focused at the fibre's proximal end and transmitted to the sensing material located at the fibre's distal tip. Light emitted from the fluorophore is captured and carried back through the fibre. After exiting the proximal end, the light is filtered and projected onto a charge-coupled device (CCD) camera. The recorded intensities are proportional to the fluorescence at each individual fibre position. Modern cameras have CCD chips with megapixel resolution. High resolution is necessary to differentiate an imaging fibre's miniature feature sizes (3 μm). CCD cameras provide high quantum efficiencies and low dark current noise, which optimises the signal-to-noise ratio. The low dark current enables longer acquisition times without a significant noise increase. By employing a less intense light source in tandem with a CCD camera, photobleaching associated with laser excitation is limited, without sacrificing the detection capabilities. In addition, laser excitation sources can be expensive and have fixed excitation bandwidths. A computer-controlled system can use scripted programs to allow rapid transfer between wavelengths and filter sets. This rapid transfer ability enables multiple wavelengths to be used for real-time analysis of multiple fluorescent indicators.

3 Sensor fabrication methods

Sensors were fabricated by attaching the sensing chemistries to the fibre optic microarray platform using three general approaches: homogenous sensor/polymer layers, discrete polymeric sensing regions, and microsphere-based sensors. The three sensor fabrication approaches vary in their complexity and

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provide different levels of parallel interrogation. The extent of parallel interrogation depends on the sensing region dimensions, with the smallest feature corresponding to a single fibre in the bundle.

3.1 Polymer sensing layers

The first sensing format involves coating the entire distal fibre face with a sensing layer. The sensor is comprised of a specific indicator chemistry attached to a polymer layer. The sensing layer is attached directly to the fibre, forming a thin polymer film (from 5 to 100 µm) so it remains optically transparent.

To attach the sensing layer to the fibre, the glass fibre surface is first derivatized to incorporate functional groups compatible with the polymer. For example, fibres can be treated with 3-(trimethoxysilyl)propyl methacrylate for copolymerisation into a methacrylate polymer matrix.[3] The surface-derivatized fibre is then coupled to the sensing layer by two different methods: photoinitiation or dip coating polymerisation. Photoinitiation entails immersing the fibre in a prepolymer solution containing monomer, initiator, crosslinker, and indicator, and then initiating polymerisation by delivering light through the fibre to the fibre's distal face. In this method, polymer forms directly on the fibre surface while the bulk solution remains unpolymerised. Dip coating the fibre involves immersing the pre-functionalised fibre into a prepolymer/indicator solution. When the fibre is removed from the prepolymer, the polymer coating formed on the fibre surface functions as the sensing layer. In either case, all polymerised sensing regions produce a uniform distribution of indicator, as determined by visualization of the fluorescence intensity on the fibre face.

Polymerisation of a sensing layer on a single core fibre allows only a single parameter to be measured. When an imaging fibre bundle is coated with a uniform sensing layer, each individual fibre in the bundle acts as an independently addressable sensor, providing an array of sensors. With both single core fibres and imaging arrays, the sensing film thickness influences the sensor response time.

3.2 Discrete polymer sensors

A second sensor fabrication technique involves polymerising discrete sensing regions at specific locations on the fibre face. This method allows multiple sensors to be immobilized on a single fibre array. The sensing regions are fabricated using chemistry identical to the photoinitiated polymer coating sensors described above. Multiple polymeric sensing regions are fabricated on the same fibre, with each single sensor region having dimensions between 20–100 microns in diameter (Figure 4). Different sensor regions are created via the photoinitiation light focused to discrete areas on the fibre's proximal end. Only the areas exposed to the photoinitiation light form a photopolymer on the distal fibre face. By exposing separate regions of the fibre face to different photopolymers, different sensing chemistries can be incorporated onto a single imaging bundle. While this format enables multiple sensing regions to be addressed in parallel, the total number of unique sensors that can be assembled on a single fibre is limited because the individual sensor sizes are relatively large as they encompass multiple fibres.

3.3 Microwell arrays

Fibre optic bundles also serve as a platform for a high density ordered microwell array.[4] This sensor fabrication method addresses the need for higher levels of parallel sensing and high throughput analysis. Microwells are formed based on the

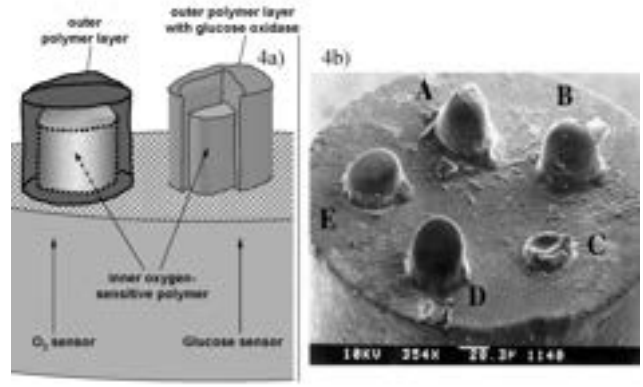

Fig. 4 a) Schematic diagram of the discrete glucose sensing regions. The inner polymer contains the oxygen sensitive indicator. One outer polymer coating is doped with glucose oxidase. 4b) Scanning electron micrograph of the triple sensor CO_2(A and B), pH (C), and O_2(D and E). The pH sensor collapsed due to water evaporation when subjected to high vacuum during the gold coating process. Reprinted from "Simultaneous monitoring of pH, CO_2, and O_2 using an optical imaging fiber", J. A. Ferguson *et al.*, *Anal Chim. Acta*, 1997, **340**, 123, © 1997 with permission from Elsevier Science.

compositional differences between the core and clad materials, which allow the cores to be selectively etched, forming a patterned array of wells (Figure 5). The microwells have

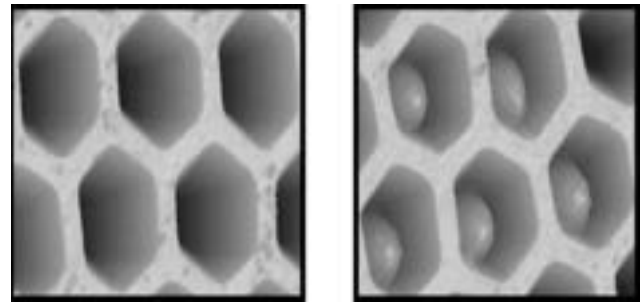

Fig. 5 Atomic force micrographs of etched fibre bundles (left). Each well is 3 microns in diameter. The wells can be filled with complementary-sized microspheres derivatized with different sensing chemistries (right).

diameters equal to those of the cores from which they were formed, with the relative depths dependant on the fibre composition, etchant concentration, and exposure time. These wells can be loaded with complementary-sized microspheres containing a variety of incorporated sensing materials. The microsphere sensors consist of silica or polymeric microparticles containing fluorescent indicators or derivatized with specific recognition elements, such as single stranded oligonucleotides. The fibre core diameters and microwell depths can be tailored to complement a variety of sensing materials. In addition to microspheres, individual cells have been employed as sensing materials. For cell-based sensing, a number of different cell types can be loaded onto arrays, including yeast (*Saccharomyces cerevisiae*),[5] bacteria (*Escherichia coli*),[5] and mouse fibroblast cells.[6] Some cell types can be genetically modified, offering more flexibility in sensor design. The genetic modifications make available indicating cells that respond to their environment. Cell-based sensor arrays are described in more detail below in the biosensors and biomonitoring section. In either microsphere or cell-based arrays, multiple sensor types can be added to the etched fibre face to form the array. When the arrays are fabricated, the sensor addition process is random, so sensor placement is unknown. After fabrication, the random array requires a registration process such that the positions of each sensor in the array can be determined. Sensor array decoding schemes are described in the next section. The random self-assembly process dictates that sensor arrays are formed

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with multiple replicates of each sensor type to ensure representation, which also provides a signal averaging benefit. Signal averaging of many identical sensors, increases the total signal-to-noise ratio by the square root of the number of sensors examined. In addition, replicate sensors in the array minimize potential false positive and false negative signals by confirming the signal response. The simple sensor fabrication protocol and miniature sensor size allow enormous numbers of sensor arrays to be made at one time. A single batch of sensors is enough to fabricate thousands of arrays; one millilitre of sensor stock contains 10 billion identical microsphere sensors so that it is easy to fabricate arrays with identical sensing behaviour.

The miniature sensor feature size also directly affects the sensor packing density, sensitivity and experimental throughput of the resulting array. Higher packing density results in smaller overall array sizes and interrogation of small sample volumes. The same number of target molecules in a smaller volume yields a higher local concentration, making it possible to detect a small absolute number of molecules.

3.3.1 Array decoding. The array self-assembly process results in sensors randomly dispersed into the microwells, so an optical decoding system is required.[7–9] To ascertain the position of multiple sensor types in a randomised array, the sensing elements are encoded with fluorescent dyes prior to array fabrication. Sensor encoding links each specific sensor type with a unique fluorescent indicator pattern. Encoding dyes must have emission spectra separate from those of the indicators used for sensing. By employing multiple fluorescent dyes with multiple dye intensities, hundreds of different microsphere sensor types can be encoded with different optical "bar codes".

The encoding dyes can be incorporated into the microspheres via three different methods: adsorption, covalent attachment, or internal entrapment. Adsorption methods are dependant on the microsphere compositions and surface functionality, as well as the dye's structure. Covalent attachment requires compatible functional groups between the microsphere and dye, which can be used to link the two species. Internally trapped dyes are introduced into polymeric microspheres in the presence of organic solvents. The solvents swell the polymer, allowing the dye to penetrate into the particle interior. Upon solvent evaporation, the dye is trapped in the polymeric matrix. In this method, it is important that the encoding dyes are insoluble in the solvent in which the measurements are to be performed.

4 Applications

Imaging fibre bundles are an ideal platform for multiplexing because they contain thousands of individually addressable light pathways. Each fibre is aligned with a spatially discrete sensing region that can be used in a sensor array format. In this fashion, every sensing region in the bundle can be interrogated simultaneously. The sensor microarrays are used in numerous applications, described in the following sections.

4.1 Combined imaging and sensing

Imaging fibre sensor arrays can be used for combined imaging and sensing. In this application, a sensing layer is coated uniformly onto the fibre's distal tip. A thin polymer coating is deposited so that light can still be transmitted readily through the sensing layer. Each fibre transmits a signal originating from the sensing region at its distal tip. When imaging bundles are used to transmit images, each fibre conveys a small part of the image. The coherent nature of the bundle enables the individual fibre pixels to be assembled into an entire image (Figure 6). The

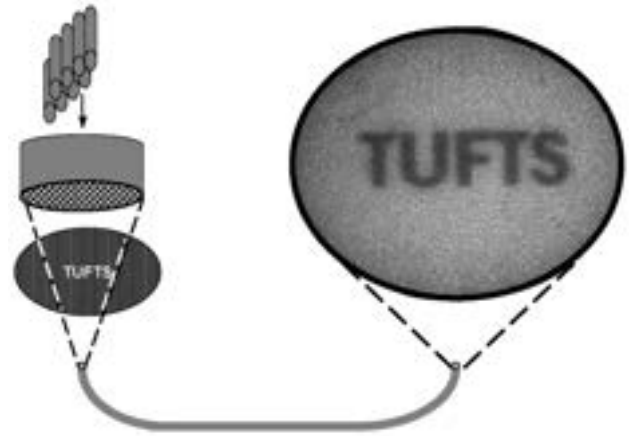

Fig. 6 Coherent imaging bundles. Fibre optic imaging bundles are comprised of fused single core fibres. Thousands of individual 3 micron fibres can be bundles in a 500 micron diameter bundle. The bundles can be used to transmit an image, where each individual fibre in the bundle acts as a single pixel of the image.

imaging system is capable of switching between white light and a specific indicator wavelength. Because each fibre conveys both white light and a fluorescent signal originating from the sensing layer, a fibre optic bundle can be used for both imaging and sensing. Imaging fibres used in white light mode can be used to visualize samples and to control sensor placement, while the appropriate excitation and emission wavelengths can be used to interrogate the immobilized indicator. Employing an imaging bundle to visualize the changes links the physical changes with the fluorescent intensity measurements. A major advantage with this approach is that no exogenous indicator is added to the solution providing for relatively unperturbed measurements. The spatial resolution is determined by the individual fibre's pixel size and can be less than one micron.

Combined imaging and sensing was performed on live cells.[10] Sea urchin eggs, upon fertilization, undergo a Na^+/H^+ exchange with their environment. This cation exchange mechanism releases H^+ from the cell, forming a pH gradient to prevent additional sperm from reaching the egg. This fibre optic sensor array was coated with a pH sensitive polymer layer to monitor local pH changes while simultaneously visualizing structural changes, including cell division. The pH sensitive fluorescent indicator seminaphthofluorescein (SNAFL) was covalently attached to the polymer layer. Fluorescein and its derivatives, such as SNAFL, have both acid and base forms with separate excitation wavelengths (440 nm/490 nm, respectively), but a single emission wavelength (530 nm). The acid form of fluorescein has minimal fluorescence but its conjugate base strongly fluoresces, so a ratiometric measurement of the base and acid intensities (490/440) could be used to avoid sensor drift. The imaging system was programmed to enable both excitation wavelengths to be measured continuously. Within a minute of sperm addition, the fluorescence intensity increased dramatically, and cell division was observed. This platform is capable of monitoring multiple cells simultaneously at physiological conditions, without compromising the cell membrane.

4.1.1 Corrosion monitoring. Corrosion was also monitored with a fibre optic pH sensor.[11,12] The sensor array was brought proximal to a metal surface, to measure the release of H^+ from discrete regions on the surface where corrosion took place. Localized corrosion was measured while white light images of the damaged areas of the corrosion surface were viewed simultaneously. Imaging fibre sensors were employed to monitor crevice, pitting, and galvanic corrosion. By simultaneously measuring and visualizing corrosion patterns, information related to corrosion rates and inhibition processes could be obtained. Fluorescence intensity changes were observed, signalled by a pH sensitive dye response (fluorescein iso-

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thiocyanate, FITC) to the electrochemical generation of local H^+ or OH^- concentrations. H^+ ions were formed at the anode due to solvolysis of the anodic metal, and OH^- was formed at the cathode based on the reduction of water and/or oxygen. Areas with large fluorescence intensity changes were imaged with a fibre positioned a few microns from the metal surface, and ratiometric fluorescence measurements were performed. The fluorescent responses were confirmed by surface imaging with atomic force microscopy (AFM) to map topographic changes.

Corrosion sites were monitored for the formation and passivation of crevices and corrosive pitting.[11] Metals such as iron and nickel are oxidized in the presence of chloride ions, resulting in pH changes. A stainless steel surface was immersed in 0.1 M KCl (pH 6.6) and subjected to a potential of +0.5 V vs. saturated calomel electrode. Deviations from the background pH were seen concomitant with visualized narrow fissures. Regions of increased fluorescent intensity correlated with circular craters 10–20 µm in diameter. These crevices and pit regions were indicative of localized corrosion (Figure 7).

Fig. 7 Image monitoring pH after 20 minutes of an optical fibre pH sensor array over an aluminium surface. Darker regions correspond to areas of lower pH. Reprinted with permission from S. Szunerits and D. R. Walt, *Anal. Chem.*, 2002, **74**, 886. © 2002 American Chemical Society.

Corrosion was also viewed with the Cu/Al galvanic pair in slightly acidic media. In this case, the reduced species was again oxygen/water, but Al metal was now being oxidized. The applied constant anodic potential was +0.2 to +0.5 V. The measured fluorescence changes were proportional to the applied potential. Higher buffer concentrations were more damaging to the surface, corroborated by the rougher surfaces viewed in the AFM images. The same galvanic pair was used to visualize the effects of corrosion with different indicators.[12] SNAFL was covalently attached to the polymer matrix and a constant anodic potential (0.4 V) was applied. Fluorescence intensity decreases were seen due to decreases in pH, similar to those seen with FITC. Areas of marked pH differences were observed, followed by a return to the buffer pH value indicative of surface passivation. The extent of corrosion was also monitored with an aluminium sensitive indicator, morin, which results in a substantial fluorescence increase when complexed with Al^{+3}. Initially, morin was used free in solution, but it was also immobilized to the polymer layer along with a pH sensitive dye. Immobilizing the morin improved the ability to monitor the spatial and temporal corrosion effects. The sensor provided a linear kinetic corrosion profile for concentrations of 0.5–5.0 mM, and was reusable for over 100 assays. Two known corrosion inhibitors were also investigated, $CeCl_3$ and 8-hydroxyquinone (8HQ). Inhibitors would be expected to show decreases in current and smaller areas of active corrosion, indicative of surface passivation. For example, $CeCl_3$ adsorbs to the surface, forming a metal oxide passivation layer. At 3.0 mM $CeCl_3$, the current decreased from 50 to 20 µA within one minute, resulting in lower measured pH changes (0.4 pH units as compared to 0.9 uninhibited). In addition, corrosion sites were observed to be approximately half the size as those formed without inhibitors present. The 8HQ also inhibits corrosion of aluminium and demonstrated substantially better inhibition qualities than $CeCl_3$. Active corrosion sites were 1/10 the size of corrosion sites observed without the inhibitor, and the pH change decreased to 0.15 units versus the 0.9 unit decrease observed in the solution without inhibitor. With 8HQ, the entire surface was passivated within 20 minutes.

4.2 High-density discrete sensing regions

An improved method for preparing discrete photodeposited sensing regions could be performed by employing the individual fibre pixels as the pathways for photoinitiation.[13] Whereas the previously described methods used photoinitiation light focused onto the fibre face, an improved photoinitiation method was developed that directed photoinitiation light through the fibre itself.[14] Building off of this methodology, thousands of oxygen and pH sensors were formed in parallel, each precisely aligned with an individually addressable fibre[13] (Figure 8). The polymerisation process was similar to that

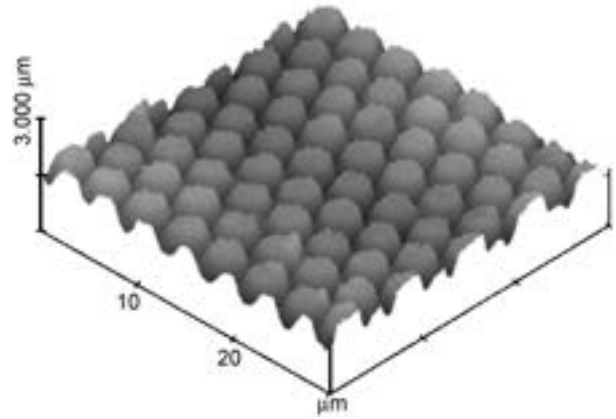

Fig. 8 Atomic force micrograph of a polymer layer pattern from a chemically-etched imaging fiber. Polymerization was initiated with light traveling through the fibre bundle, resulting in an array of 3 micron diameter polymer sensor spots. Reprinted with permission from B. G. Healey and D. R. Walt, *Anal. Chem.*, 1997, **69**, 2213. © 1997 American Chemical Society.

described previously, except the photoinitiation system provided more control over the light intensity and exposure time. The polymerised sensing regions had dimensions of 2.8 µm diameter, with 0.6 µm and 1.2 µm heights for pH and oxygen regions respectively. The pH and O_2 sensors are described in detail in section 4.4. A principal advantage of this method is the hemispherical shape of the miniature sensing regions, which enable radial diffusion, and a more rapid sensor response time. The pH sensor responded to a difference of 1.5 pH units within 300 milliseconds, and the oxygen sensor measured a 90% change from its steady state value in less than 200 milliseconds.

4.3 Artificial olfaction

Traditional sensing approaches require one sensor for every analyte. As the number of analytes to be measured increases, the

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array becomes more complex and the possibility for interference grows. An alternative sensing approach is based on principles derived from the mammalian olfactory system. Vertebrate olfaction is known to be both highly sensitive and broadly responsive to a wide range of odours. Rather than utilizing specific receptors for each different analyte, a broad assortment of odours can be sensed using cross-reactive sensor responses. Odours are defined by both their spatial and temporal patterns generated by olfactory receptors and interpreted by the neural circuitry.[15] Similar spatial and temporal responses can be generated with artificial sensory systems, mimicking the cross-reactive nature and neural networking associated with olfaction.

Fluorescence-based fibre optic sensor arrays have been developed, modelled after these olfaction principles.[3, 16–22] Semi-selective, cross-reactive sensors were fabricated to imitate the broad responses of the vertebrate olfactory receptors.[16,19] The functionally diverse sensors were incorporated into polymer matrices on single core fibres as previously described. Bundling multiple single core fibres allowed multiple sensor types to be interrogated simultaneously. This platform provided a simple fabrication protocol, rapid response and low detection limits. Other artificial olfaction systems have been developed[23] using a variety of sensing methods, including conductive polymer,[24,25] surface-acoustic wave,[26,27] and electrochemical schemes.[28,29] Many of these techniques suffer from poor sensor reproducibility, low sensitivity, and slow sensor response.

For the fibre-optic artificial olfaction system, the sensors are comprised of a solvatochromic dye indicator immobilized in a variety of polymers. Solvatochromic dyes shift their fluorescence emission spectrum based on their local environment. The most common solvatochromic dyes red-shift their emission spectrum as polarity increases. Changes in the fluorescence emission spectrum, in turn, affect the quantum efficiency, spectral shape, fluorescence lifetime and the wavelength maximum of the indicator. Each of these optical properties can be simultaneously measured with the fibre optic imaging system. Figure 9 shows fluorescence emission spectra from a dye immobilized in a polymer and exposed to different organic vapours. As can be seen, the more polar the vapour, the more red-shifted is the emission spectrum. The dye's initial microenvironment is defined by the polymer's polarity.[16,17] The analyte vapour diffuses into the polymer layer, influenced by

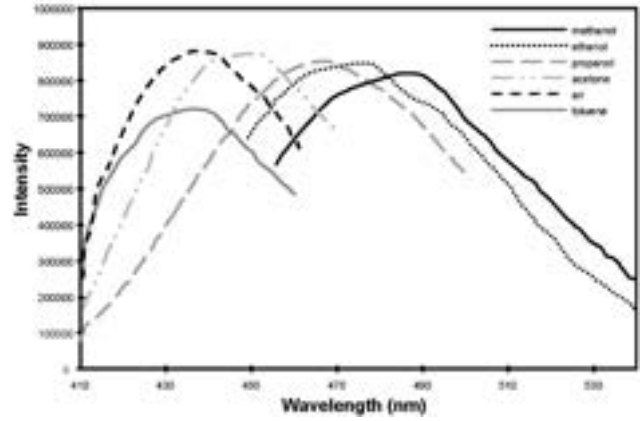

Fig. 9 The solvatochromic effect. Fluorescence emission spectra of a single dye immobilized in a polymer and exposed to different organic vapors. The spectra get more red-shifted with increasing polarity of the vapor.

polymer swelling, hydrophobicity, and adsorption efficiency. By incorporating the same dye into multiple polymers with different polarities, a distinct response pattern is generated for each analyte. Upon exposure to a vapour pulse, vapour diffuses into the polymer and changes its polarity. This polarity change is reported by the solvatochromic dye. Because different vapours diffuse into the polymers at different rates, the temporal responses of the different sensors in the arrays are monitored. To illustrate the different sensor responses, Figure 10 shows the responses of four different sensors exposed to four different analyte vapours. These responses are measured at a single wavelength.

The first generation of fibre optic artificial olfaction employed 300 μm diameter single core fibres coated with different polymer layers to trap the dye Nile Red.[3,16] Nineteen different fibres were bundled to form an array. The advantage of Nile Red as an indicator is that it is soluble in numerous solvents and is relatively photostable. Experiments were performed using the array to discriminate various organic compounds (alcohols, esters, aromatics, etc.), as well as mixtures and concentrations. For each analyte, the different sensors varied in their temporal response shape. Artificial neural networks were trained to detect and identify each analyte. Although identification was not correct 100% of the time, a high degree of differentiation was

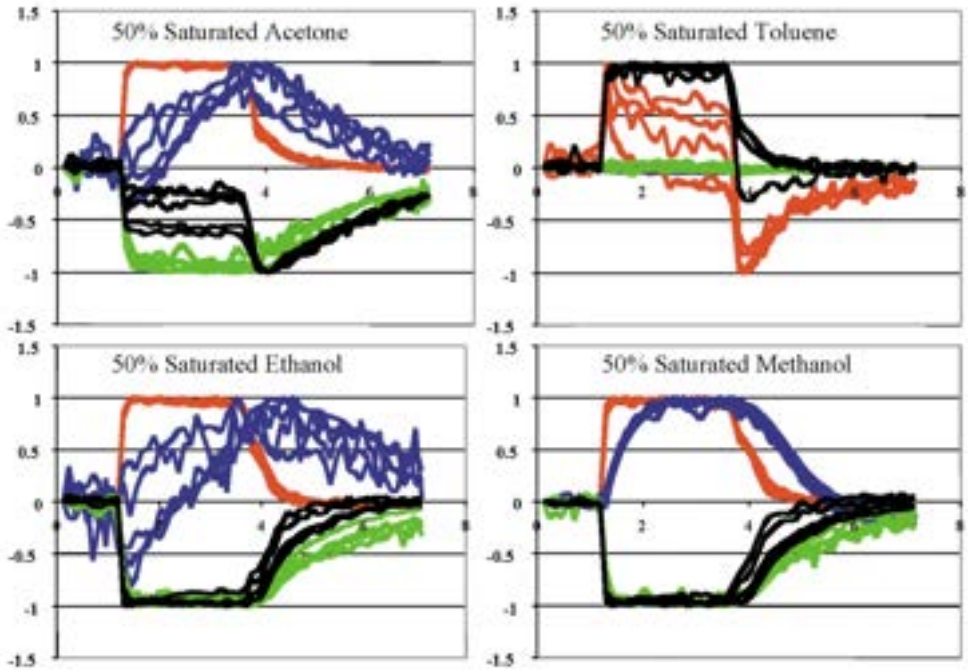

Fig. 10 Four different sensors and their response to four analytes, plotted as normalized fluorescent intensity versus time (s). Note: These responses are monitored at a single wavelength.

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observed, and analytes could be detected at concentrations down to 1000 ppm.[3] The array demonstrated millisecond response times. The sensors were stable for weeks and over hundreds of trials. Successful analyte classification from optimised neural networks trained on the temporal responses provided substantial improvement over those generated from integrated fluorescent signals demonstrating the value of using dynamic responses rather than equilibrium values.[16]

Similar experiments were performed using a more advanced classifying algorithm.[18] A learning vector algorithm proved to be more appropriate for pattern recognition applications and provided more reliable analyte classification. The experiments addressed a larger, more diverse pool of analytes and mixtures. Sensor responses were pre-screened to eliminate sensors with minimal responses. A total of 12 sensor-types were employed for 20 analyte vapours. Corrections were made for humidity differences, and responses were normalized to remove concentration dependent effects. A series of descriptors, such as slopes, maximum intensity changes, and average intensity values per unit time, were used in the algorithm. Discrimination and quantification of training sets and external prediction sets were improved over the initial results, approaching 100% classification.

4.3.1 High-density microsphere-based artificial olfaction. While initial artificial olfaction research incorporated discrete polymeric sensing regions, the contemporary design has supplanted the various sensor types with 3 µm fluorescently dyed microspheres.[19–22] Different microsphere compositions perform similar to the polymer layers, providing unique microenvironments for the dye and analyte vapour to interact. By employing microspheres composed of different materials, such as silica or a variety of polymers with different surface and internal functionality, a diverse sensor stock was made. Sensors are randomly distributed into the microwell array, and the response of each microsphere/indicator combination to a particular vapour is used for positional registration. Sensor placement, although random, is easily determined and linked with its response. In this fashion, the dye serves two purposes and the microsensors are termed "self-encoding". The random sensor distribution more closely mimics that of the olfactory epithelium, where primary odour receptor cells are randomly distributed.[30]

The introduction of self-encoded microsphere sensors has revolutionized fibre optic artificial olfaction.[19–22] The miniature sensor feature size provides a more rapid response and higher sensitivity. Miniature sensors provide more surface area for vapour interactions. Micro-sensors also allow a greater sensor packing density compared to other platforms. The sensor loading capacity along with the array fabrication method provides inherent sensor redundancy similar to vertebrate olfaction systems. This redundancy provides a signal to noise amplification that increases as $n^{1/2}$, where n is the number of sensors examined. The positive signal effect is illustrated in Figure 11. Figure 11(a) shows the responses of 39 individual microsensors compared to their summed response. Figure 11(b) illustrates the noise associated with a single microsensor versus the average response of 39 sensors. Array detection limits are determined by taking advantage of signal averaging. Averaging the 39 identical microsensors afforded a sixfold enhancement in signal-to-noise ratio compared to a single sensor, comparable to the theoretical value. A toluene sample (840 ppb, 0.002% in air) was readily detected with signal-summing microspheres, but was undetectable for any single microsensor. Separate arrays were examined months apart, but still maintained their characteristic responses.[19]

These microsphere-based arrays have been applied to the detection of volatile organic compounds (VOC), nitroaromatic explosives-like materials (NAC) and complex mixtures. Self-encoded microsphere-based arrays were fabricated containing equal distributions of six different microsensor types, with approximately 2500 microsensors in total.[20] Analytes included three varieties of coffee beans, acetone, toluene, and 1,3-dinitrobenzene. A classification rate of 100% was obtained for the samples using discriminant function analysis algorithms. Experiments were also performed using specific sensors determined to be effective for detecting explosives-like compounds.[21] The NACs were hidden in complex background vapours at much higher concentrations (10^5 times) to simulate more realistic detection situations. The array provided strikingly different response profiles for such compounds as 4-nitrotoluene, 2,4-dinitrotoluene and 1,3 dinitrobenzene. The

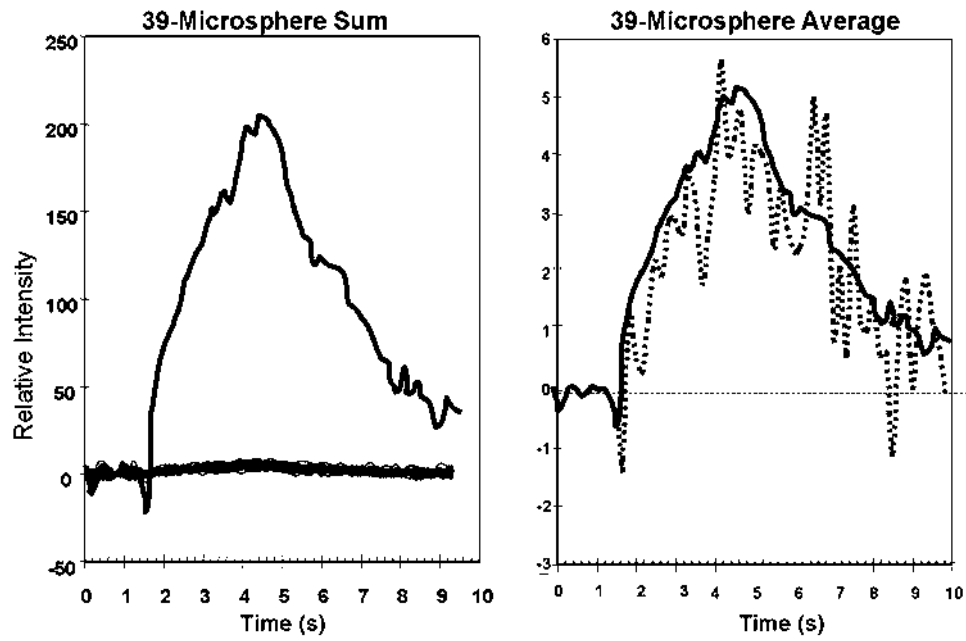

Fig. 11 Signal amplification through microsphere summing—response to 1% methanol vapor in air. Summation of 39 microsphere responses versus the individual microsphere responses (left). The average of the 39 microsphere responses (right). The dotted trace is a single arbitrary microsphere response scaled for comparison and showing how the noise can be virtually eliminated by summing. Reprinted with permission from T. A. Dickinson et al., *Anal. Chem.*, 1999, **71**, 2192. © 1999 American Chemical Society.

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characteristic response patterns were retained with sample concentrations between 5 ppb–215 ppm. At these levels of analyte, the detection capabilities are affected more by vapour delivery than by the sensor sensitivity.

The microsphere sensor technology has also improved array-to-array reproducibility.[22] The problem with all previous artificial olfaction arrays is that they eventually lose their ability to respond, resulting in a need to retrain the classifier on the next array. The lack of array reproducibility is partially due to inherent batch-to-batch differences in the fabrication of polymer-based sensors. To counteract this problem, billions of identical microsphere-based sensors are fabricated simultaneously, providing a more homogeneous sensor stock. For analysing multiple arrays fabricated from a single sensor stock, a flexible classifying algorithm was employed to account for minor differences in the response features that affect sensor reproducibility. The classifier corrected for sensor artefacts and assigned values for the discrimination confidence level. In an analytical challenge to detect low-level NACs, different arrays have demonstrated high reproducibility and transfer of a trained classifier across arrays. The ability to transfer the training from array-to-array allows entire arrays to be replaced without retraining, and moves the system towards a database of learned responses similar to odour memory.

4.4 Biosensors and biomonitoring

Biosensors contain a biological recognition element that converts a binding or catalytic event into a detectable signal. As an example, it is possible to prepare a sensor for acetylcholine using the enzyme acetylcholinesterase. In this approach, acetylcholinesterase catalyses the hydrolysis of acetylcholine to choline and acetic acid. The resulting acid can be detected readily by a pH indicator located proximal to the enzyme. An optical sensor for acetylcholine was fabricated by copolymerising a pH sensitive dye and the enzyme into a polymer coating on the distal face of an imaging fibre bundle.[31] Acetylcholineesterase was co-immobilized with fluorescein isothiocyanate (FITC) into a poly-(acrylamide-*co*-*N*-acryloxysuccinimide) matrix on the imaging fibre face. The residual amine and *N*-hydroxysuccinimide ester groups in the polymer react with the FITC and surface lysine residues of the esterase, respectively. Ratiometric fluorescein-based measurements were employed as described above. Sensor response depends on substrate diffusion into the polymer matrix; the acetylcholine sensor provided a rapid (<1 second) response to physiologically significant analyte concentrations.

A similar biosensor was fabricated using the discrete sensing region approach, where dual sensors for pH and penicillin monitoring are fabricated on the same fibre bundle.[32] The enzyme penicillinase, which converts penicillin to penicilloic acid, was co-immobilized with a fluorescein derivative in a discrete polymer region on the fibre face. As the enzyme converted penicillin to penicilloic acid, the pH decreased, resulting in a fluorescence intensity decrease that is monitored via ratiometric fluorescein measurements. The penicillinase was incorporated into the polymer matrix as lyophilised micrometer sized enzyme particles. Upon hydration of the matrix, the enzyme activity was restored. The sensor demonstrated sub-millimolar detection limits for penicillin. Because this sensor responds to both a change in penicillin concentration as well as a pH change, it is necessary to control the pH of the solution being measured. Alternatively, by including a separate pH-sensing region to independently determine the solution pH, measurements of more complex environments where the pH changes over time were possible. This biosensor scheme can be adapted to any other enzyme-based method that generates or consumes protons.

An optical biosensor for combined oxygen and glucose sensing was also fabricated with discrete photopolymerised regions.[33] This dual sensor was fabricated via successive rounds of photopolymerisation. The oxygen-sensing region consisted of an initial 27 µm diameter polymer spot, coated with a second 54 µm diameter polymer layer (Figure 4a). The inner polymer region was embedded with an oxygen sensitive ruthenium(II) dye [both tris(2,2′-bipyridyl ruthenium(II) chloride) and tris(phenanthroline ruthenium(II) chloride) were used] and subsequently coated with a second gas permeable polymer layer containing glucose oxidase. The glucose oxidase reaction consumes oxygen. A decrease in oxygen concentration results in increased fluorescence intensity from the interior ruthenium indicator. The fluorescent signal was dependent on both glucose and oxygen concentrations, therefore the glucose sensors were used in combination with oxygen sensors that measured the solution oxygen concentration, analogous to the dual sensor described above. The sensor's dynamic range was dependent on the amount of enzyme incorporated in the second polymerisation step, and could be tailored to suit a variety of glucose concentrations.

An imaging fibre that contained three different sensing regions was fabricated for simultaneous measurements of O_2, pH and CO_2.[34] Each sensing region was photopolymerised as discrete sites on the end of a single fibre bundle (Figure 4b). The pH and oxygen sensor chemistry has been described above. The oxygen-sensing region was initially polymerised without the ruthenium dye, followed by exposure to a dye/solvent solution that infuses the dye into the polymer. This fabrication method avoids potential dye photobleaching in the photoinitiation step. Preparing the oxygen sensor first avoids exposing the other sensing regions to the ruthenium dye. The carbon dioxide sensor was prepared by immobilizing a fluorescein derivative in a polymer matrix, identical to the pH sensing regions. The polymer region was then saturated with a bicarbonate buffer solution and coated with a hydrophobic polymer. As carbon dioxide crosses this hydrophobic membrane, the pH decreases due to the carbonic acid reaction, resulting in a decreased fluorescence response from the interior pH sensitive region. In this fashion, the pH and CO_2 are both measured using the ratiometric method. All three sensors are reversible, and the CO_2 sensor is unresponsive to changing oxygen concentrations. This triple sensor was used for monitoring beer fermentation. Prior to the addition of yeast, all analyte levels remained constant. Upon yeast addition, all three sensors immediately responded as glucose was partially oxidized to carbon dioxide, oxygen was consumed and the pH decreased (Figure 12).

4.4.1 Oligonucleotide detection. Nucleic acids have inherent base-pair recognition capabilities that can be implemented as detection elements. Oligonucleotide recognition capabilities were first combined with electrophoretic gels for radiolabeled detection via the Southern method.[35] Fibre optic platforms now serve as a novel platform for fluorescence-based oligonucleotide detection.[8,36–43] Oligonucleotide sequences can be aligned directly with individual fibres in a fibre bundle, allowing parallel, high throughput analysis of genomic samples. The immobilized single-stranded sequences, or probes, are capable of recognizing their complementary sequence counterparts, or targets, from a complex solution. Because optical fibres are amenable to fluorescence-based techniques, combining single-stranded oligonucleotides with optical fibres allows fluorescence-based methods to be used in place of the once standard radiolabel detection. A number of methods exist that can incorporate fluorescence into the probe-target pair. Fluorescence can be integrated directly into the target sequence via the polymerase chain reaction (PCR). PCR methods incorporate a fluorescence label either from fluorescent nucleotides or via fluorescently-labelled primer sequences used to initiate the PCR reaction, resulting in fluorescently-labelled, amplified target

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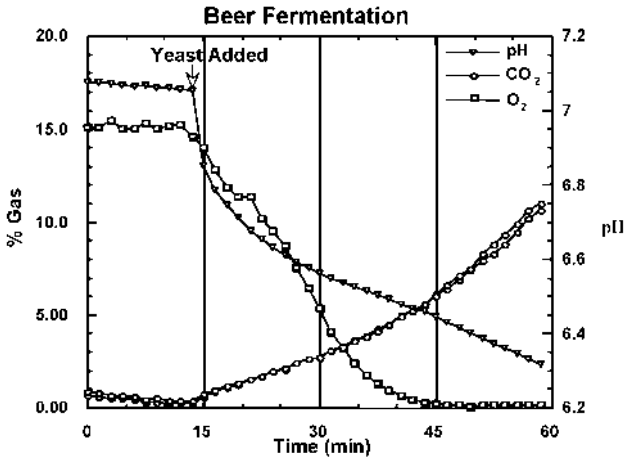

Fig. 12 Sensor responses for pH, O_2 and CO_2 sensors monitoring beer fermentation. Response changes occurred after the addition of yeast. Sensor reproducibility is demonstrated by the identical CO_2 curves from two CO_2 sensors in the array. Reprinted from "Simultaneous monitoring of pH, CO_2, and O_2 using an optical imaging fiber", J. A. Ferguson *et al.*, Anal. Chim. Acta, 1997, **340**, 123, © 1997 with permission from Elsevier Science.

species. The PCR amplification process can also be used to concentrate specific mRNA transcripts from a complex sample, allowing transcripts of known importance to be identified. This method has become standard, and is important when sample amplification is necessary for detection. This labelled primer method can also be employed for reverse transcription (RT) assays to form cDNA (DNA complementary to mRNA transcripts that are being measured) while retaining their relative expression levels in the tissue. The cDNA formed in the RT process is also more stable than the transcript mRNA. Other methods exist to incorporate fluorescent dyes into nucleic acids, such as intercalating dyes or fluorescence resonance energy transfer (FRET) methods. Intercalating dyes bind to double stranded DNA, providing signal after the oligonucleotide duplex is formed. FRET methodology is a distance dependent fluorescence quenching method that will be described later under the molecular beacons section. In each case, correct probe-target hybridisation generates a fluorescence response. Fluorescence-based assays are extremely sensitive, and duplex formation can be controlled to interrogate single base differences, which can serve as important markers for genomic comparison or known genetic variations.

As with the artificial olfaction sensors, the first generation of oligonucleotide sensors involved polymeric sensing regions.[37,38] Single-stranded oligonucleotide probe sequences were attached to discrete photopolymerised regions on an imaging fibre's distal face.[38] The array was capable of demonstrating single base discrimination, and could interrogate submicrolitre sample volumes. Since DNA duplexes have a specific melting temperatures associated with dissociation, the probe-target pairs could be denatured, restoring the oligonucleotide probes to their single-stranded forms for reuse. This oligonucleotide array was regenerated with elevated temperature and repeated on the same fibre for three consecutive assays. Oligonucleotide arrays could also be fabricated on single core fibres (200 µm diameter). The ssDNA probes were coupled directly to a polymer covering the fibre cores.[37] Multiple single core fibres were then bundled to provide a parallel detection scheme. The bundled array demonstrated the ability to profile gene products amplified via PCR. This scheme also enabled the detection of unlabeled target molecules. The oligonucleotide arrays were first exposed to fluorescently-labelled synthetic targets that hybridised with the ssDNA, supplying the array with an initial fluorescent signal. The unlabeled target sample was then hybridised to the same array to displace the pre-hybridised fluorescent species, resulting in a fluorescence decrease. The fluorescence decrease was proportional to increasing concentrations of the unlabeled sample target solutions. The probes were regenerated by exposure to organic denaturants or elevated temperatures. These assays provided a rapid, reusable platform for oligonucleotide detection.

4.4.2 High-density microsphere-based oligonucleotide arrays. The magnitude and complexity of the human genome epitomize the need for nucleic acid detection technology that is rapid and efficient at detecting a large number of genetic differences. Array platforms have advanced the reproducibility and consistency of large-scale nucleic acid detection by enabling high throughput parallel analysis. Typical oligonucleotide microarrays use thousands of gridded microscopic single-stranded (ss) DNA spots arranged on a solid substrate, and as such, are platforms suitable for simultaneous genetic analysis of a complex target solution. For example, many molecular events are dependent on a cluster of genes or a series of gene networks. The expression profile of diseased tissue could be matched against healthy control tissue to determine relevant gene transcripts that are differentially (up- or down-) regulated. The target DNA from the two different tissue samples can be labelled with different fluorescent dyes to compare the hybridisation ratios.[44] The extent of hybridisation generates signals that relate directly to the abundance, or expression level, of each transcript. The concept of a gridded ssDNA array has developed into a number of notable platforms over the last decade, including those fabricated by ink-jet deposition[45] and photolithography.[46,47] Comprehensive reviews of fluorescence-based nucleic acid detection and microarrays have recently been published.[2,44]

The second generation of fibre optic DNA arrays incorporated microsphere sensors as the individual sensing elements.[8,9,36] The principle is similar to the described microsphere arrays used in artificial olfaction, except the sensing elements are ssDNA probe sequences attached to the microsphere surface. As described above, billions of identical sensors can be made simultaneously.[7–9] Microsphere encoding is required for positional registration and enables the user to differentiate large numbers of different DNA probe types in the microwell array.

While this fibre optic microsphere-based array platform is comparable to other DNA array detection schemes, it has a few major advantages. The platform is regenerable, with the ability to use a single array for dozens of assays while many other arrays can be used only once. This platform has a simple, flexible fabrication protocol. The fabrication process allows customizing the numbers of sensors in the array. Greater numbers of identical sensors can be added to improve the signal-to-noise ratio and offset the occurrence of false positive and false negative signals. As new sequences of interest are discovered, they can be attached to microspheres and added to the existing sensor pool to be incorporated into new arrays. This microsphere-based platform has the smallest element sizes (3 µm) of any array format, which provides a greater sensor packing density ($\sim 2 \times 10^7$ microsphere sensors per cm^2) and smaller overall feature sizes. By keeping the overall dimensions of the array extremely small, smaller volumes of sample are needed. DNA hybridisations are diffusion dependent, so the same number of target molecules in a smaller volume yields a more rapid response, increasing the experimental throughput. The miniature feature sizes also provide a detection advantage. By confining target molecules to a small volume, a high local concentration is achieved. For example, a few hundred target molecules confined to a 3 µm well of approximately 30 femtolitres volume relates to nanomolar concentration. Nanomolar concentrations are readily detectable using fluorescence. The next several sections will describe the use of the imaging fibre microwell array as a unique platform for oligonucleotide-based assays.

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Multiplexed arrays were used with twenty-five different microsphere-types to detect different cystic fibrosis mutations and cytokines.[8] The arrays could monitor hybridisations in real time, and nanomolar concentration hybridisations could be detected within a few seconds. A single array was reused over 100 times with minimal signal differences between hybridisations, and array regeneration was completed upon 1 second exposures to denaturants.

Additional experiments were performed to determine the array's detection limits.[36] The number of microsensors in the arrays have a dramatic effect on the detection limits, which can be controlled to suit the experiment (Figure 13). As with the

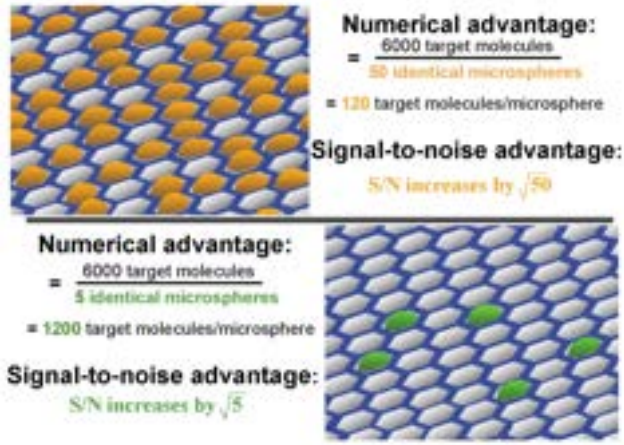

Fig. 13 The effects of increasing numbers of microspheres in the array.

artificial nose, greater numbers of identical microsensors provide a signal-to-noise (S/N) advantage, increasing the S/N ratio based on the number of identical sensors in the array. Conversely, fewer sensors provide a numerical advantage because as hybridisation goes to completion, the same absolute number of target molecules hybridised to fewer microspheres would provide more target molecules per microsphere and a higher, more easily detected signal. This concept has enabled a zeptomole detection limit (~600 molecules), the lowest detection limit of any array platform. Experiments were performed with a 10^9-fold excess of irrelevant DNA without affecting the detection limits. Other methods to detect such small total target molecule numbers require lasers and confocal optics, while the fibre array system employs a white light source and CCD camera.

The third generation of DNA microarrays developed with the fibre optic platform also employs microsphere-based sensing elements, but with a modified DNA detection methodology. The microsphere-based array platform has been combined with both molecular beacons[40] and aptamers.[39] Both schemes utilize the inherent recognition capabilities of nucleic acids, but take advantage of a nucleic acid sequences' ability to adopt different three-dimensional conformations.

4.4.3 Molecular beacons. Fluorescence resonance energy transfer (FRET) is a technique incorporated into the fibre optic sensor array platform for detection of unlabeled target molecules.[40,48] FRET uses a donor fluorophore coupled to an acceptor chromophore. The efficiency of donor to acceptor energy transfer is determined by their separation distance and spectral overlap. When the donor and acceptor are proximal, the acceptor reduces the donor fluorescence by one of two methods. First, an acceptor can be a quenching molecule, designed to non-radiatively stifle the donor fluorescence. Second, the acceptor can possess an excitation band overlapping the donor's emission wavelength. In this instance, the excited donor fluorophore is returned to the ground state and its energy is transferred to the acceptor emission. This donor/acceptor FRET design has been combined with nucleic acid probe sequences for molecular beacon sensor arrays.

Molecular beacons tether the donor and acceptor molecules to opposite termini of a single-stranded oligonucleotide probe sequence. The oligonucleotide sequence consists of a recognition segment, flanked by short complementary ends. In the absence of a target complementary to the recognition sequence, the two flanking sequences hybridise to form a stem-loop structure (Figure 14a). This conformation brings the donor and

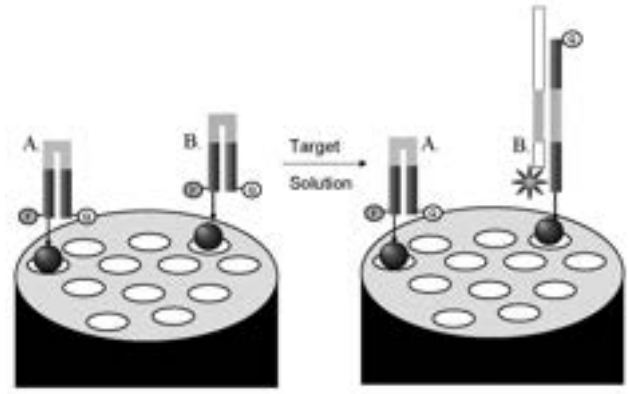

Fig. 14 Molecular beacons. In the absence of target molecules complementary to the loop structures, the beacons remain in a hairpin formation, the fluorophore (F) and quencher (Q) remain close, and fluorescence is quenched. Upon complementary target binding, the beacon opens, allowing F to fluoresce uninhibited.

acceptor in proximity and the donor's fluorescence is reduced. Binding between the molecular beacon recognition segment and its correct single-stranded target, unfolds the stem-loop structure and spatially separates the donor and acceptor. This separation allows the donor signal to fluoresce uninhibited (Figure 14b), and signals the presence of the complementary oligonucleotide target.

Fibre optic microarrays utilizing molecular beacons were used for label-less detection of cystic fibrosis gene targets.[40] Fluorescein and 4-(4-dimethylaminophenylazo)benzoic acid were employed as the fluorophore and quencher respectively. The molecular beacon arrays provided a rapid response capable of quantitative measurements of target solutions. This platform is regenerable and has a picomolar detection limit. Label-less detection provides a simpler, faster protocol that can analyse unpurified solutions, limiting excessive sample manipulation, without the need for extra sample handling necessary for PCR-based label incorporation.

4.4.4 Aptamers. Aptamers are nucleic acid recognition sequences selected from a random library based on direct interaction with a target molecule or protein.[49,50] Aptamer development involves successive cycles of screening a combinatorial aptamer library followed by enrichment for those sequences exhibiting the desirable binding characteristics. The binding characteristics are based on each aptamer's unique three-dimensional structure. The aptamer library is exposed to target molecules tethered to a solid support, binding those with the preferred interactions, while any non-interacting sequences are washed away. The retained sequences are isolated, amplified and subjected to successive screening cycles of increasing stringency. In this manner, only those few candidates with the greatest affinity for the target molecule are selectively enriched.

Nucleic acid aptamers are natural choices for recognition elements because they are selected to interact with specific target molecules. Targets to which aptamers have been selected include small proteins or other similar sized molecular species, with binding monitored via techniques such as surface plasmon resonance[51] or absorbance spectroscopy coupled with capillary

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electrophoresis.[52,53] A fibre optic microarray was fabricated with aptamers specific for thrombin, an important biomolecule in blood clotting.[39] Aptamer arrays provide quantitative signal responses to fluorescently-labelled target solutions. Detection of unlabeled target samples is preferable because labelling samples requires additional labour. Unlabeled thrombin also was detected down to 1 nanomolar concentrations in a competitive assay similar to the general microsphere-based DNA method described above. The arrays were reusable over multiple assays, with assays completed in 15 minutes, including regeneration of the array.

5 Cell-based microarrays

Fibre optic arrays can also employ living cells as the sensing elements positioned in the etched fibre wells (Figure 15). Cell-based arrays provide a unique sensing method compared to other multiplexed sensing schemes, because live cells can respond to a wide variety of biologically significant compounds. Cell responses are either physiological or genetic. Physiological responses are based on local environmental changes such as pH, O_2 and CO_2. Genetic responses link a promoter gene with an adjacent reporter gene that codes for an optically detectable biomolecule. The biomolecule's signal response corresponds to the promoter's expression level. The promoter's expression can be affected by multiple parameters, including environmental conditions and cellular metabolic processes that regulate (up- or down-) promoter expression. Because the promoter is linked to the reporter gene, the fluorescence response correlates to the conditions that affect the promoter activity.

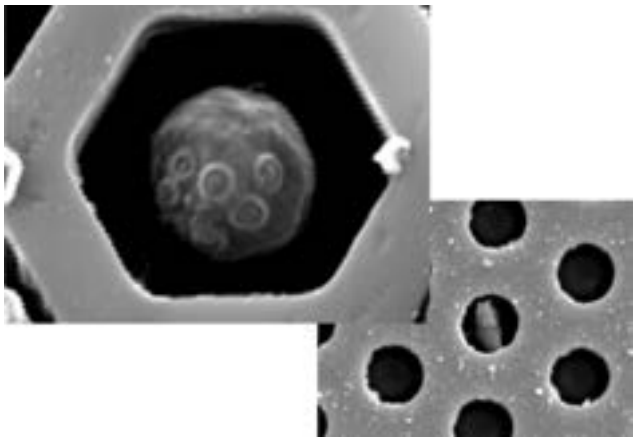

Fig. 15 Cells in wells. The microwells can be tailored to match the size of different cells, including yeast (left) and bacteria (right). Reprinted with permission from I. Biran and D. R. Walt, *Anal. Chem.*, 2002, **74**, 3046. © 2002 American Chemical Society.

While many other cell-based assays are limited by the accuracy and reproducibility of the analytical measurements, the optical fibre platform allows non-invasive, repetitive measurements of thousands of individual live cells simultaneously. This platform provides a simple indexing, mapping, and fabrication protocol, and once fabricated, an array does not require manual sample manipulation. Because cells localize randomly into the etched microwells, they are encoded with dyes to positionally register each specific cell type. By employing several dyes or dye ratios, multiple different cell lines/strains can be addressed in parallel, further increasing the experimental complexity in a simple, directed manner. The cell responses can be measured individually, or as an average response. Interrogating each cell individually is beneficial because each cell has a different metabolic rate and is at a different stage of its life cycle. Cell viability is not compromised, and neither physical indexing nor sequential scanning are required. Experimental reproducibility can be validated with cell replicates in the array. A single assay can provide a massive amount of information and can be used for high throughput screening (HTS) drug discovery applications.

Initial fibre optic cell-array research employed mouse fibroblast NIH 3T3 cells as the sensing elements located in the microwell array.[6] Cells were encoded via standard lipophilic dye kits, allowing the dye to passively diffuse into the cell membrane. The encoding dyes are not cytotoxic and are rapidly incorporated into the cells. The cells adhere to the well bottoms, and are positionally mapped via their internal dyes. Cell viability is confirmed with standard Live/Dead assay kits. These kits demonstrate cell viability based on non-specific enzyme processes and membrane permeability. For live cells, dye precursors diffuse into the cell interior and are converted to fluorescent species by non-specific enzyme processing. In this case, the generation of a fluorescent signal indicates cell viability. Fluorescent indicators that denote dead cells, such as DNA intercalators, are unable to permeate intact cell membranes and do not provide a signal for live cells. Non-viable cells have compromised membranes that allow these dyes to intercalate with the cellular DNA and generate a signal indicative of cell death.

These types of cell arrays were used to measure cell metabolism based on extracellular pH changes. Arrays were combined with 100 nm sized particles embedded with a pH-sensitive fluorescent dye. The nanoparticles were immobilized in a polymer layer at the bottom of the microwells before loading the array with cells and were incapable of reaching the cell interior. The nanoparticles were added in concentrations such that numerous nanoparticles accumulated in each well. The microwells containing individual cells exhibited a fluorescence decrease as cell metabolism leads to an extracellular pH decrease. Nanoparticles occupying wells without cells did not exhibit any fluorescence change. This pH sensitive cell array system is capable of measuring cell responses affected by O_2, CO_2 and glucose, among others.

A second generation of cell arrays utilized an advanced encoding strategy.[5] Concanavalin A was conjugated to multiple fluorescent dyes that were used to encode yeast cells (*S. cerevisiae*) via binding to mannoproteins present on the cell wall. This methodology could also be used for other available surface protein/fluorescent dye pairs. Bacterial cells (*E. coli*) can also be engineered to express different fluorescent proteins that can be employed for encoding. Plasmids encoding naturally fluorescent biomolecules, such as green fluorescent protein and its variants, were incorporated into the cells. Experiments were performed using three different optically detectable proteins, but the potential exists to scale up the number of unique genetic encoding signatures by using other combinations of commercially available plasmids.

This second generation of cell-based array assays was developed taking advantage of cell-engineering techniques. Engineered yeast cells containing the reporter *lacZ* gene coding for the enzyme β-galactosidase were used. β-galactosidase is not an optically detectable species, but processes a precursor substrate added to the medium into a fluorescent molecular signal. The yeast cells utilized the *lacZ* reporter gene expression in combination with a known two-hybrid system. Two hybrid systems regulate their reporter response on the basis of specific protein–protein interactions. The extent to which the two proteins interact affects the transcription level of the reporter gene, which mediates the fluorescent response. The two proteins are introduced into the cell via plasmids; a binding domain encoding one protein and an activating domain in a second plasmid. When the two coded proteins interact, a transcription factor complex is activated, initiating transcription of the reporter gene downstream of the binding site. For these cell-based assays, the two-hybrid system was based on the

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interaction of large T-antigen proteins, p53 and SV40. Three cell strains were investigated; a positive strain expressing the correct hybrid pair, a negative strain expressing non-interacting proteins, and a wild type strain without the two-hybrid system. The majority of positive responses were linked to the positive strain, with a few negative strains also exhibiting a fluorescence increase. The wild type strains did not exhibit any fluorescence response.

This cell-array platform can provide a rapid, repetitive analysis of live cell metabolic responses, and is a valuable tool for HTS. The miniature array size enables interrogation of smaller volumes with lower reagent costs, often a concern in cell-based HTS processes. Arrays can also be patterned into a 96- or 384- matrix. The matrix positions can then be paired with the wells of microtitre plates, such that multiple identical arrays can be screened in a microtiter plate format simultaneously, further increasing the throughput.

6 Conclusions

Fibre optic imaging bundles are a universal sensing platform capable of numerous sensing schemes, ranging from relatively simple pH sensors, to high-throughput cell-based screening. Imaging fibres enable combined imaging and sensing that relates physical changes with responses monitored by the sensor. Fibre optic imaging arrays possess miniature feature sizes, allowing high-density sensor packing ($\sim 2 \times 10^7$ sensors per cm^2). The miniature feature sizes enable a fast response and more sensitive measurement capabilities. The platform's versatility in experimental design is exemplified by the multiple methods developed for fabricating sensing regions. The array platform can be tailored to suit the experimental design, whether it is for monitoring single analytes or for more complex assays, including artificial olfaction, DNA detection, or cell-based screening. While a number of schemes have been described in this review, the indicators or other parameters can be adapted to suit other sensing designs, allowing these array formats to be further exploited for other specific applications.

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Subject Re: CONFIDENTIAL AND PRIVILEGED RE: Walt Papers

From Francis Barany <barany@med.cornell.edu>

To: George Barany <barany@umn.edu>

Cc: Robert Hammer <rphammer@gmail.com>, Pearson, Matthew <mpearson@akingump.com>, Valerie Cross <vlc1@cornell.edu>, Monib Zirvi <matzirvi@yahoo.com>

Date Feb 27, 2016 at 3:30 PM

Dear GB,

This is exactly the paper we needed.

No further comments via email.

Thanks a million,

Love, FB

> On Feb 27, 2016, at 3:14 PM, George Barany <barany@umn.edu> wrote:
>
> see attached
>
> please confirm that's what you want
>
> On Sat, Feb 27, 2016 at 11:19 AM, Francis Barany <barany@med.cornell.edu> wrote:
>
> > Dear Monib, George, and Bob,
> >
> > Monib, thank you for finding this - excellent.
> >
> > The reason I had not sent this paper to Matthew and Valerie previously is that I am not able to access it through PubMed — i.e. it is not available at Weill Cornell Medicine Library.
> >
> > George and Bob — would you be able to access this through your Chemistry department or personal subscription to ACS? (Valerie: ACS —

personal subscription to ACS? (Valerie: ACS = American Chemical Society — not Cancer).

Whoever gets it first, please email to all.

Most appreciated!

Francis

[redacted]

On Feb 27, 2016, at 11:11 AM, Monib Zirvi <matzirvi@yahoo.com> wrote:

Dear All,

Note the use of the words "Universal" and "addressable" in this review article.

Fluorescence-based fibre optic arrays: a universal platform for sensing.

Review article

Epstein JR, et al. Chem Soc Rev. 2003.

Authors

Epstein JR[1], Walt DR.

Author information

[1]Max Tishler Laboratory for Organic Chemistry, Department of Chemistry, Tufts University, Medford, Massachusetts 02155, USA.

Citation

Chem Soc Rev. 2003 Jul;32(4):203-14.

Abstract

Optical fibres provide a universal sensing platform as they are easily integrated with a multitude of different sensing schemes. Such schemes enable the preparation of a multitude of sensors from relatively straightforward pH sensors, to more complex ones, including artificial olfaction sensors, high-density oligonucleotide arrays, and high-throughput cell-based arrays. Imaging fibre bundles comprised of thousands of fused optical fibres are the basis for an optically connected, individually addressable parallel sensing platform. Fibre optic imaging bundles possess miniature feature sizes (3-10 micron diameter fibres), allowing high-density sensor packing (approximately 2 x 10(7) sensors per cm2). Imaging fibre bundles transmit coherent images enabling combined imaging and sensing, relating the responses monitored by the sensor to observable physical changes. The individual fibre cores can also be selectively etched to form a high-density microwell array capable of housing complementary sized microsensors. The miniature feature sizes facilitate a faster response and more sensitive measurement capabilities. The platform is extremely versatile in its sensing design, allowing the sensing scheme to be tailored to fit the experimental design, whether for monitoring single analytes or more complex multiplexed assays. A number of sensing schemes and applications are

described in this review.

PMID 12875026 [PubMed - indexed for MEDLINE]

Sent from my iPhone

--
George Barany
Distinguished McKnight University Professor of
Chemistry
University of Minnesota
Department of Chemistry
[redacted]
<b300617d.pdf>

Subject Re: Confidential Status Report regarding Cornell University, et al. v. Illumina

From Francis Barany <barany@med.cornell.edu>

To: Monib Zirvi <matzirvi@yahoo.com>, Valerie Cross <vlc1@cornell.edu>, Pearson, Matthew <mpearson@akingump.com>

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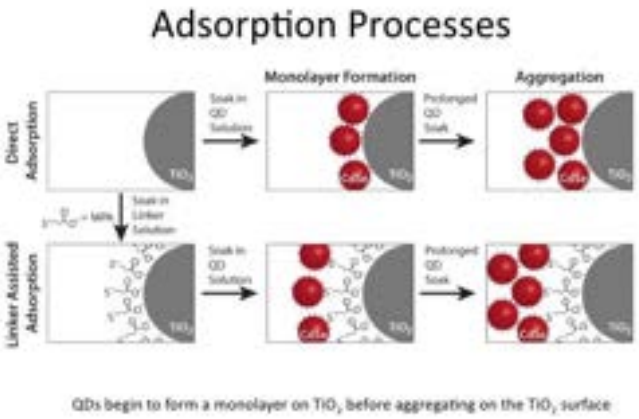

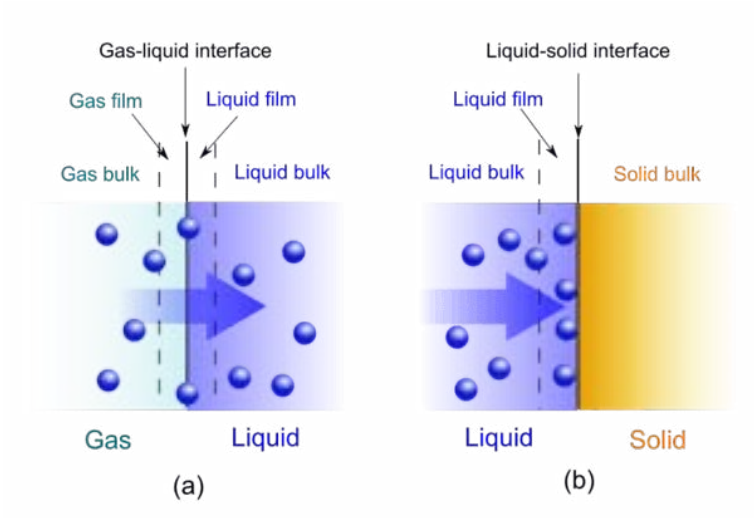

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> [redacted]

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We will keep you informed of significant developments.

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Cornell University
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Brian Kelly, Ph.D., CLP
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<5-6-2016 CU v. Illumina-Report & Recommendation.pdf>
<Summary of R&R for Inventors.pdf>

Subject RE: Confidential Status Report regarding Cornell University, et al. v. Illumina

From Maria Kempe <maria.kempe@med.lu.se>

To: Francis Barany <barany@med.cornell.edu>, Monib Zirvi <matzirvi@yahoo.com>, Valerie Cross <vlc1@cornell.edu>, Pearson, Matthew <mpearson@akingump.com>

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Sent: Friday, May 20, 2016 2:54 PM
To: Monib Zirvi; Valerie Cross; Pearson, Matthew
Cc: George Barany; Matthew Lubin; Robert Hammer; Maria Kempe;

Brian Kelly
Subject: Re: Confidential Status Report regarding Cornell University, et al. v. Illumina

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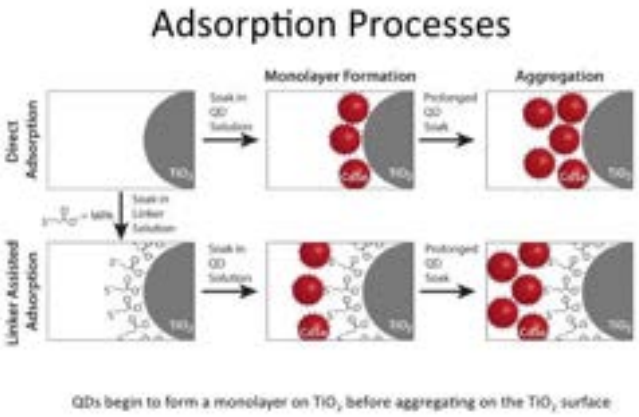
Adsorption Processes
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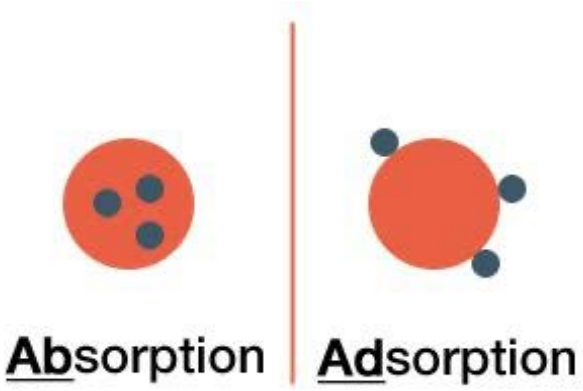
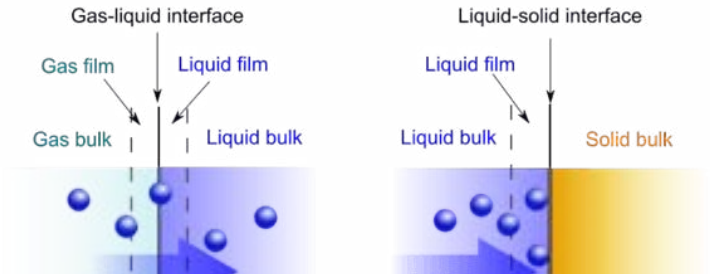
Aggregation
Direct Adsorption
Linker Assisted Adsorption
QDs begin to form a monolayer on TiO_2 before aggregating on the TiO_2 surface


Absorption
Adsorption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Gas film
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Gas bulk
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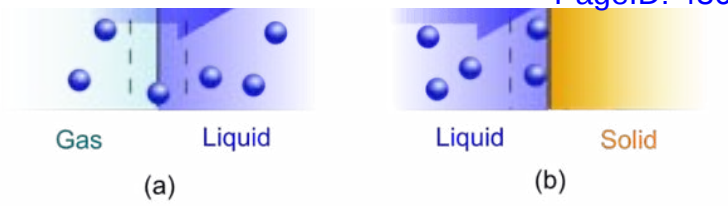

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View less

Kempe comments on Markman.doc

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Sending the file also as a pdf in case the formatting gets strange.

Best regards,
Maria

From: Francis Barany [barany@med.cornell.edu]

Sent: Friday, May 20, 2016 2:54 PM

To: Monib Zirvi; Valerie Cross; Pearson, Matthew

Cc: George Barany; Matthew Lubin; Robert Hammer; Maria Kempe; Brian Kelly

Subject: Re: Confidential Status Report regarding Cornell

University, et al. v. Illumina

Dear Monib, (& Valerie),

Monib, thank you, the "Adsorption Processes" diagram is extremely helpful

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Bob, GB, and Maria — kindly reply all, or email Valerie separately — but you must include Valerie in any communication on this to maintain confidentiality.

Valerie, I hope this helps,

Francis

[redacted]

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[redacted]

On May 19, 2016, at 5:01 PM, Valerie Cross Dorn <vlc1@cornell.edu> wrote:

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Dear Inventors:

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patent infringement litigation commenced against Illumina, Civil Action No. 10-433-LPS-MPT. On February 22, 2016, we had a claim construction hearing in the United States District Court for the District of Delaware. On May 6, 2016, Magistrate Judge Thynge issued a Report and Recommendation to District Judge Stark which will be considered and ruled upon following a time period for each side to object to the recommended constructions. Any objections we wish to make must be filed by June 2, 2016.

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We do plan to make objections to some of the recommended constructions, and to the extent we have technical questions we are working with Francis Barany to clarify, and may reach out to other inventors as needed before finalizing our papers by the June 2 deadline. The case is now moving into expert discovery, and our expert reports are due July 29, 2016. Expert depositions are to be completed by November 4, 2016, and then we will move into trial preparations. We are scheduled for trial commencing July 12, 2017.

We will keep you informed of significant developments.

Valerie and Brian

Valerie Cross Dorn
Associate University Counsel
Cornell University
[redacted]

[redacted]

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View less

Cass 1994.pdf

Mosbach 1980.pdf

Subject Re: Confidential Status Report regarding Cornell University, et al. v. Illumina

From George Barany <barany@umn.edu>

To: Francis Barany <barany@med.cornell.edu>

Cc: Maria Kempe <maria.kempe@med.lu.se>, Monib Zirvi <matzirvi@yahoo.com>, Valerie Cross <vlc1@cornell.edu>, Pearson, Matthew <mpearson@akingump.com>, Matthew Lubin <lubingenetics@me.com>, Robert Hammer <rphammer@gmail.com>, Brian Kelly <bjk44@cornell.edu>

Date May 23, 2016 at 12:57 PM

I will speak to Bob at 5:30 pm EDT = 4:30 pm CDT. I have many other things going on this afternoon, not to mention there's a Beyonce concert on campus tonight that is going to wreak havoc with traffic, etc. starting already mid-afternoon. If there is a specific reference you want me to find, I can probably have it to everyone by mid-afternoon (unless of course Maria can still get it before she goes to sleep). GB

On Mon, May 23, 2016 at 11:11 AM, Francis Barany <barany@med.cornell.edu> wrote:

> Dear Maria,
>
> This is extremely helpful and very thoughtfully written on your part.
>
> Would you kindly download that reference and send to all — likewise, Bob and George, kindly let us know if there are references within the patent that bolster our case — and download and send around.
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[redacted]

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Date May 23, 2016 at 12:58 PM

looks like we had crossing e-mails. Thank you, Maria. GB

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> Please find attached the Cass paper. I have attached also the Mosbach paper, from which I copied the immobilization figure.
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> ---
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Date May 25, 2016 at 8:02 AM

Dear Matthew P., Maria, George, and Bob,

Thank you for sending around some references to the core chemists — once we've had a chance to review, I will be responsible for sending the relevant ones to Matthew P., et al.

Maria, once again, your document is very thorough. I believe it is important for Matthew P. to articulate the issue of combining a substrate and surface to form a solid support. The word substrate is used 37 times in the patent. The word surface is used 81 times in the patent. They cannot claim we did not describe this properly.

With regards to adsorption. Please write a paragraph explaining that the surface can be adsorbed to the substrate to make the solid support. You can quote any paper referenced in the '917 patent, as well as your earlier patents (but only if they were referenced). We need to clearly explain that adsorbing the surface on the substrate, wherein

the surface may or may not contain linker molecules is DIFFERENT from non-specific adsorption of of oligonucleotides onto a surface!

oligonucleotides onto a surface!

(Again the exact paragraph from the patent is: The linker molecules can be attached to the substrate via carbon--carbon bonds using, for example, (poly)tri-fluorochloroethylene surfaces or, preferably, by siloxane bonds (using, for example, glass or silicon oxide surfaces). Siloxane bonds with the surface of the substrate may be formed in one embodiment via reactions of linker molecules bearing trichlorosilyl groups. The linker molecules may optionally be attached in an ordered array, i.e., as parts of the head groups in a polymerized monolayer.
In alternative embodiments, the linker molecules are adsorbed to the surface of the substrate.)

Maria, would you kindly:

1. Fix Example C in your Figure 1 by either making multiple “spaghetti” squiggles or have it look like a fishing dense net? (Make sure you use wavy lines as in my figure 5.)

2. Make a more sophisticated version of your figure 1, wherein you have substrate + surface -> solid support, and show where the oligonucleotides are added. Please use Blue, Red, and Green colored oligonucleotides.

For example A, it will look substrate + surface -> solid support -> solid support with clumps of blue, red, and green lines (sort of a 3D view of the oligos on the solid support.)

For example B, it will look substrate + surface (= 3 beads, one with Red lines, one with blue lines, and the last with Green lines) -> solid support with the three beads (blue, red, and green) embedded into the substrate. Please make “dimples” on the substrate (just use oval shapes that are a darker shade of gray, it will look like dimples, you may need to eliminate or fix the shadow. Then when the beads are “embedded” in the solid surface, they will look like blueberries half buried in a muffin.

For example C, it will look substrate + surface -> solid support -> solid support with clumps of blue, red, and green lines on the wavy fishing lines (sort

of a 3D view of the oligos on the solid support.)

(IF you are having trouble with this figure, just do the best you can, and I will finish it. During the Markman hearing, we represented pouring beads onto a surface — in hindsight, this was a major error since the judge / interns interpreted this as the beads are lose. They are anything but lose, you can turn an array upside-down, shake it, and no beads fall out.)

3. Kindly modify and properly label my slide Figure 5: Use one or two combinations of substrates and surfaces from the Examples, and 2 - 4 combinations from the description. Please just duplicate and label each part of the drawing: glass, (name of silanizing reagent), (name of polymer), etc.

4. Kindly modify and properly label my slide Figure 5: This is technology George developed, described in the Vagner PNAS 1996 paper - but already submitted December 18, 1995, and thus was clearly completed prior to the patent submission. Use their figure 1 to guide how you label it. (GB, if you just want to label with pen, then pdf, Bob or I can label the figure.)

Please add these new figures to the enclosed powerpoint, and label it Markman_response_Figures_v02MK.pptx

Bob and GB, you may also add your figures — again, GB if you just label a printout, and pdf, send it to me or Bob, we will put into the powerpoint.

Matthew P.,

1. When do you need Maria, Bob's, and George's final comments?

2. We should set up another webex on Friday to discuss...

Most appreciated!

Francis

[redacted]

[redacted]

Markman_response_Figures_v01.pptx

ATT00001.htm

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Date May 25, 2016 at 9:58 AM

Dear Bob, George, and Maria,

Just spoke with Bob. He reminded me that Maria should point out that use of glass, polystyrene, or silica beads are just another form of the “surface”. He suggested labeling what “chemistry” the bead is made of — i.e. technically it is no different than our polymer surfaces. (See enclosed paper to see what chemistry Illumina is using, e.g. Silica — pg 875, I’ve also copied it for you below).

(Matthew P. — have they changed their bead chemistry to polystyrene? Independent of what their bead is made of, it is still the “surface”, i.e. it has chemistry

Illumina is trying to argue that their glass wells are a first solid support, and the beads are a second solid support (not covalently attached). The oligo is attached covalently to a linker — but they claim the bead is a physical object, not a chemical.

What we need to explain is that in both cases the substrate is glass, the surface is chemistry. The surface can be either attached via covalent bonds to

surface can be either attached via covalent bonds to the substrate, or adsorbed to the substrate. The linker is chemistry that is part of the surface. The linker-surface can also be either attached via covalent bonds to the substrate, or adsorbed to the substrate. The oligonucleotide is then covalently attached to the linker.

(Maria, see Fig. 2B in the attached as an example of how the beads look when buried into the fiber-optic wells — you may use this as a guide for your drawing of "Example B")

Hope this clarifies…

Best,

Francis

[redacted]

Preparation of Oligonucleotide-Linked Beads and Bead Pools

A set of 1536 universal capture oligonucleotide sequences was synthesized. Each sequence was individually immobilized on activated beads, as follows, to create 1536 bead types. Silica beads ~3 µm in diameter (Bangs Laboratories, Inc.) were amino functionalized by incubation in 2.5% 3-amino-propyl-trimethoxysilane (Aldrich) in ethanol for 1 h at RT and then activated by reaction with 2% 2,4,6-trichloro-1,3,5-triazine (Aldrich) in acetonitrile for 2 h at room temperature. Synthetic oligonucleotides labeled at the 5 terminus with a primary amine were covalently attached to the activated beads by overnight reaction at 50°C in a solution of 3 M NaCl and 100 mM sodium carbonate (pH 11). All reagents were of highest purity grade. Empirical measurements indicated that, on average, each bead carried on the order of 106 oligonucleotides. Following quality assessment,

16 of the bead types were discarded due to low signal-to-noise ratios. The remaining bead types were combined to create a pool containing 1520 functional bead types, each representing a unique capture sequence. The sequences were designed to serve as noninteracting decodable address sequences in addition to their function as probes that capture assay products from solution. They were selected to be 22 to 24 bases long with minimal crosscomplementarity, similar GC content and Tm, no runs of a single base longer than five, and low similarity to human genomic sequences.

Decoding_random_Zipcode_arrays_Gu…

ATT00001.htm

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Date May 25, 2016 at 2:36 PM

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Cc: Monib Zirvi; Valerie Cross; Matthew Lubin; Brian Kelly; Francis Barany
Subject: Re: Confidential Status Report regarding Cornell University, et al. v. Illumina

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George Barany
Distinguished McKnight University Professor of
Chemistry
University of Minnesota
Department of Chemistry
[redacted]

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Francis Barany

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(Maria, see Fig. 2B in the attached as an example of how the beads look when buried into the fiber-optic wells — you may use this as a guide for your drawing of "Example B")

Hope this clarifies…

Best,

Francis

[redacted]

[redacted]

[redacted]

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A set of 1536 universal capture oligonucleotide sequences was synthesized. Each sequence was individually immobilized on activated beads, as follows, to create 1536 bead types. Silica beads ~3 µm in diameter (Bangs Laboratories, Inc.) were amino functionalized by incubation in 2.5% 3-amino-propyl-trimethoxysilane (Aldrich) in ethanol for 1 h at RT and then activated by reaction with 2% 2,4,6-trichloro-1,3,5-triazine (Aldrich) in acetonitrile for 2 h at room temperature. Synthetic oligonucleotides labeled at the 5 terminus with a primary amine were covalently attached to the activated beads by overnight reaction at 50°C in a solution of 3 M NaCl and 100 mM sodium carbonate (pH 11). All reagents were of highest purity grade. Empirical measurements indicated that, on average, each bead carried on the order of 106 oligonucleotides. Following quality assessment, 16 of the bead types were discarded due to low signal-to-noise ratios. The remaining bead types were combined to create a pool containing 1520 functional bead types, each representing a unique capture sequence. The sequences were designed to serve as noninteracting decodable address sequences in addition to their function as probes that capture assay products from solution. They were selected to be 22 to 24 bases long with minimal crosscomplementarity, similar GC content and Tm, no runs of a single base longer than five, and low similarity to human genomic sequences.

<Cornell approach.jpg><Illumina approach.jpg><Slide with beads & oligos.jpg>

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<MK 160526 Markman_response_Figures_v01-1.pptx>

Subject Re: Confidential Status Report regarding Cornell University, et al. v. Illumina

From George Barany <barany@umn.edu>

To: Maria Kempe <maria.kempe@med.lu.se>

Cc: Pearson, Matthew <mpearson@akingump.com>, Francis Barany <barany@med.cornell.edu>, Robert Hammer <rphammer@gmail.com>, Monib Zirvi <matzirvi@yahoo.com>, Valerie Cross <vlc1@cornell.edu>, Matthew Lubin <lubingenetics@me.com>, Brian Kelly <bjk44@cornell.edu>

Date May 26, 2016 at 3:17 PM

Dear All, I am setting aside several hours tonight to review the most current from Maria, Bob, and Francis. I will be working strictly on hard copy and then scan whatever I have before going home. Tomorrow = Friday, I will have a choppy day, but expect to be able to find time to consult via phone, Skype, and/or e-mail with any of you one-on-one or in groups. GB

On Thu, May 26, 2016 at 1:57 PM, Maria Kempe <maria.kempe@med.lu.se> wrote:

> Dear All,
>
> I am sending some suggestions for Francis slides with this email. My A-B-C-picture will come later tonight. Some more photos will come tomorrow.
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> Best regards,
> Maria
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> **Cc:** George Barany; Robert Hammer; Monib Zirvi; Valerie Cross; Matthew Lubin; Brian Kelly
>
> **Subject:** RE: Confidential Status Report regarding Cornell

Subject: RE: Confidential Status Report regarding Cornell University, et al. v. Illumina

I agree – the pictures look great

Thanks, everyone, for your thoughts and work on this.

From: Francis Barany [mailto:barany@med.cornell.edu]
Sent: Wednesday, May 25, 2016 3:21 PM
To: Maria Kempe
Cc: Pearson, Matthew; George Barany; Robert Hammer; Monib Zirvi; Valerie Cross; Matthew Lubin; Brian Kelly
Subject: Re: Confidential Status Report regarding Cornell University, et al. v. Illumina
Importance: High

Dear Maria,

Very creative! I'm hungry!

I defer to Matthew P.'s thoughts on how best to use these photos, and when it will have the greatest impact.

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Distinguished McKnight University Professor of Chemistry
University of Minnesota
Department of Chemistry
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MK 160526 Markman_response_Figure…

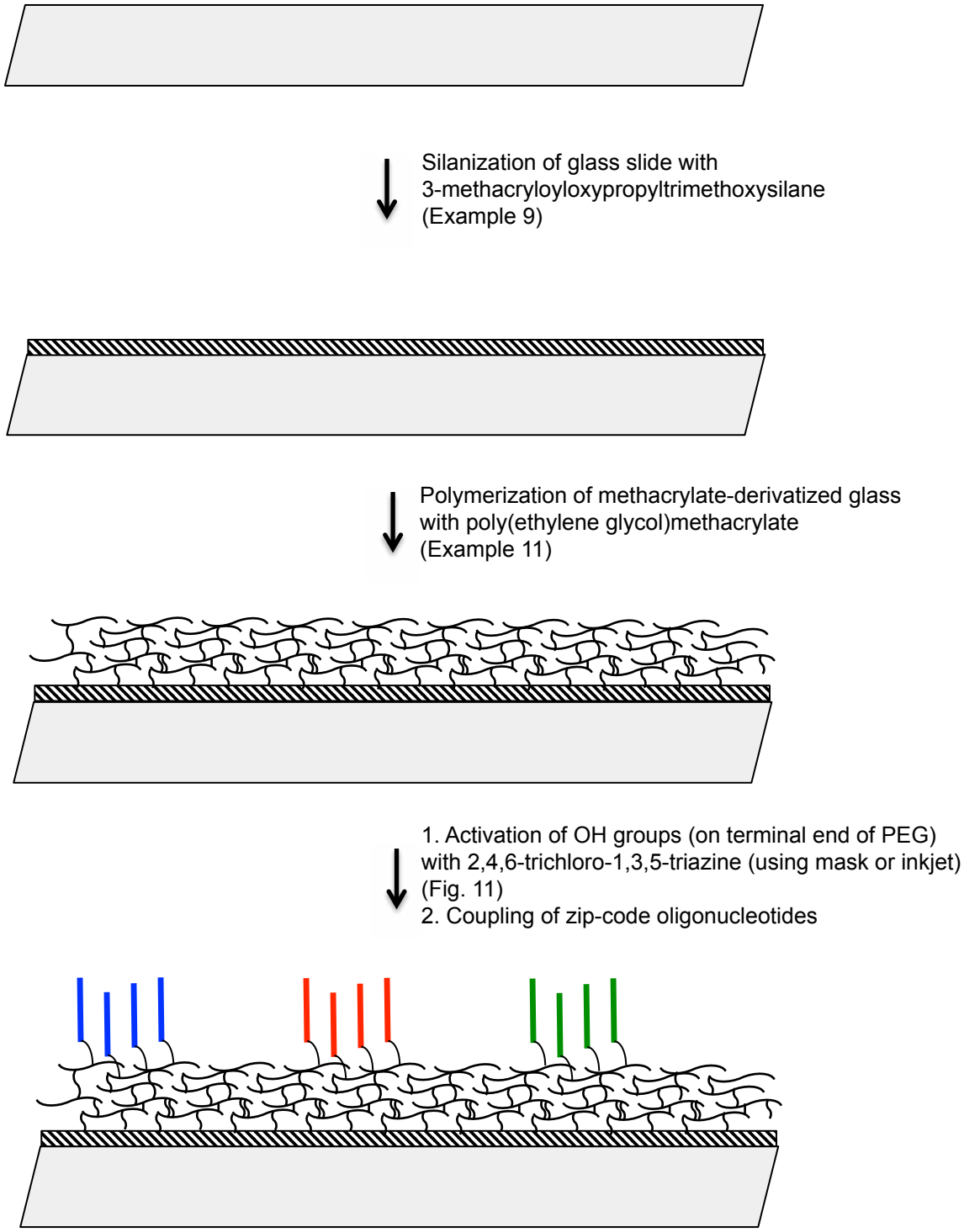
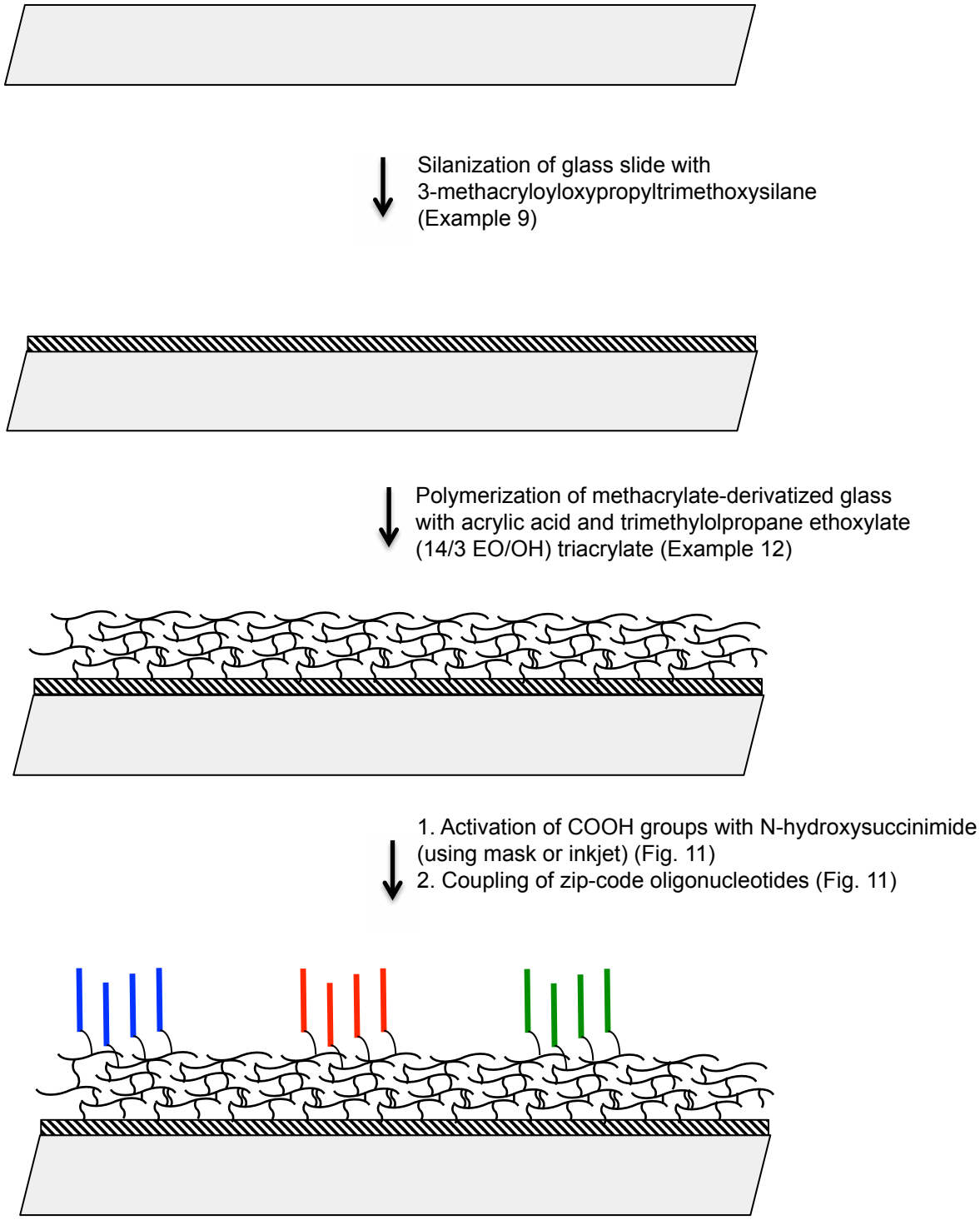

Silanization of glass slide with
3-methacryloyloxypropyltrimethoxysilane
(Example 9)
Polymerization of methacrylate-derivatized glass
with poly(ethylene glycol)methacrylate
(Example 11)
1. Activation of OH groups (on terminal end of PEG)
with 2,4,6-trichloro-1,3,5-triazine (using mask or inkjet)
(Fig. 11)
2. Coupling of zip-code oligonucleotides

Figure 5


Silanization of glass slide with
3-methacryloyloxypropyltrimethoxysilane
(Example 9)
Polymerization of methacrylate-derivatized glass
with acrylic acid and trimethylolpropane ethoxylate
(14/3 EO/OH) triacrylate (Example 12)
1. Activation of COOH groups with N-hydroxysuccinimide
(using mask or inkjet) (Fig. 11)
2. Coupling of zip-code oligonucleotides (Fig. 11)

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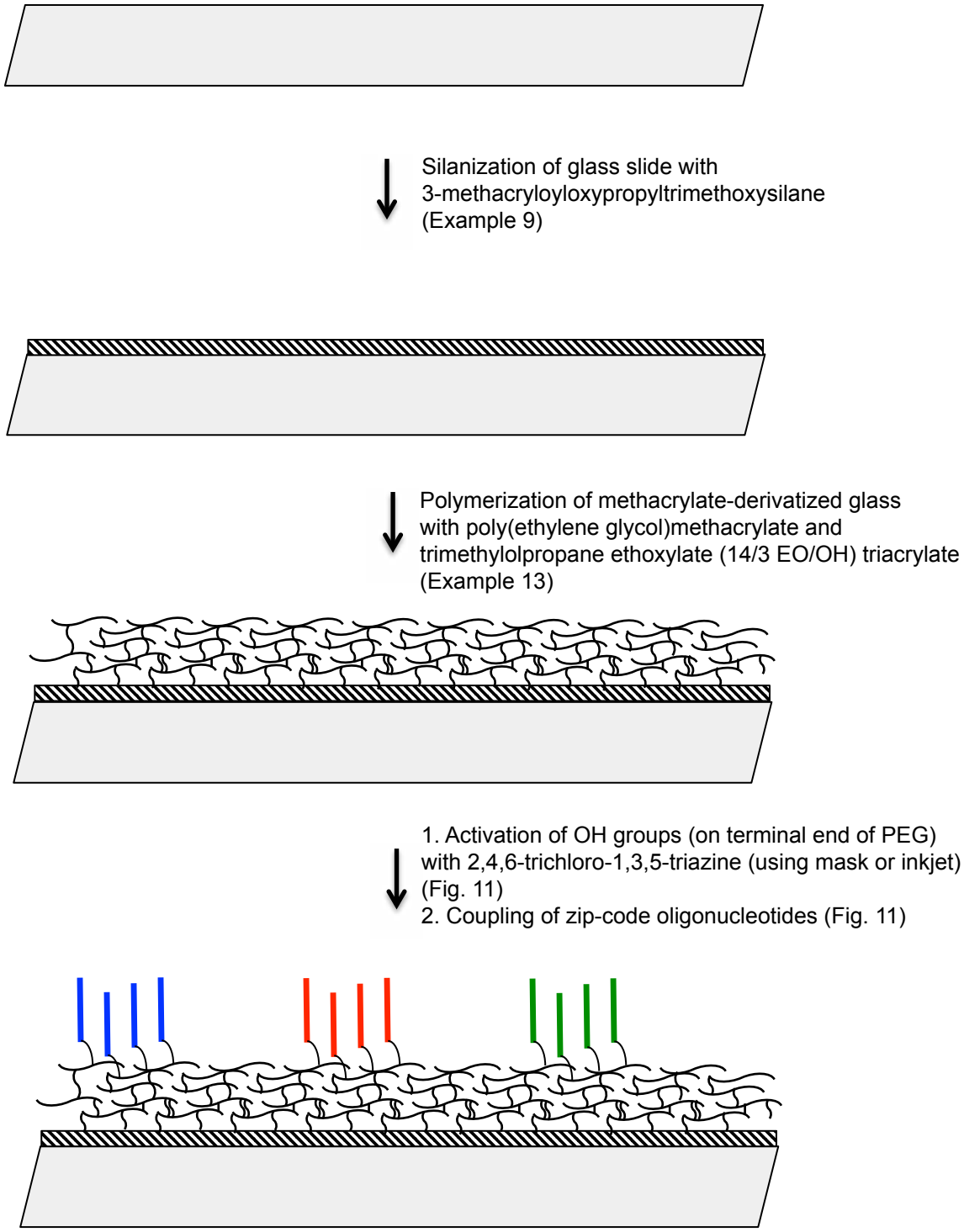
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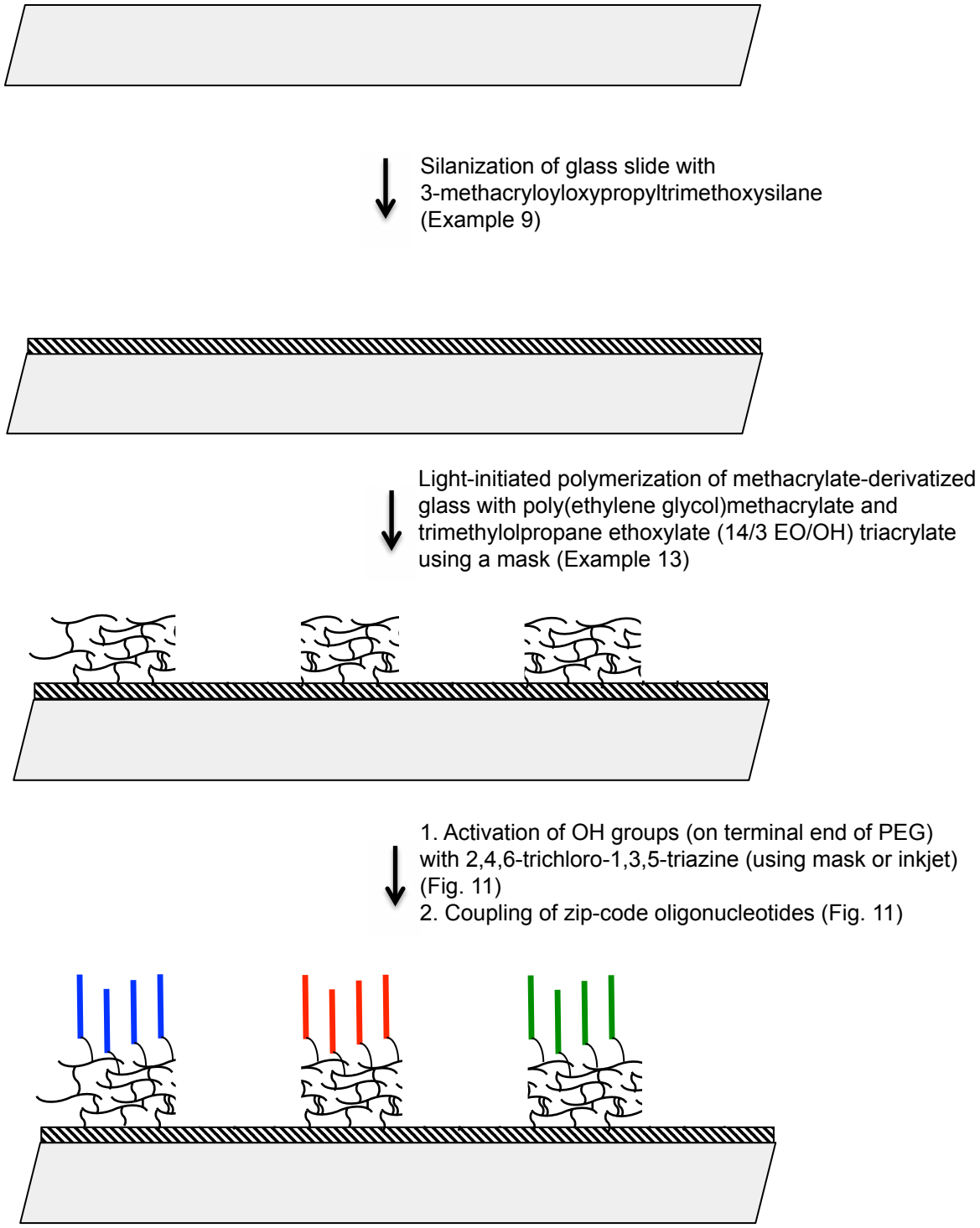
Silanization of glass slide with
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Light-initiated polymerization of methacrylate-derivatized
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trimethylolpropane ethoxylate (14/3 EO/OH) triacrylate
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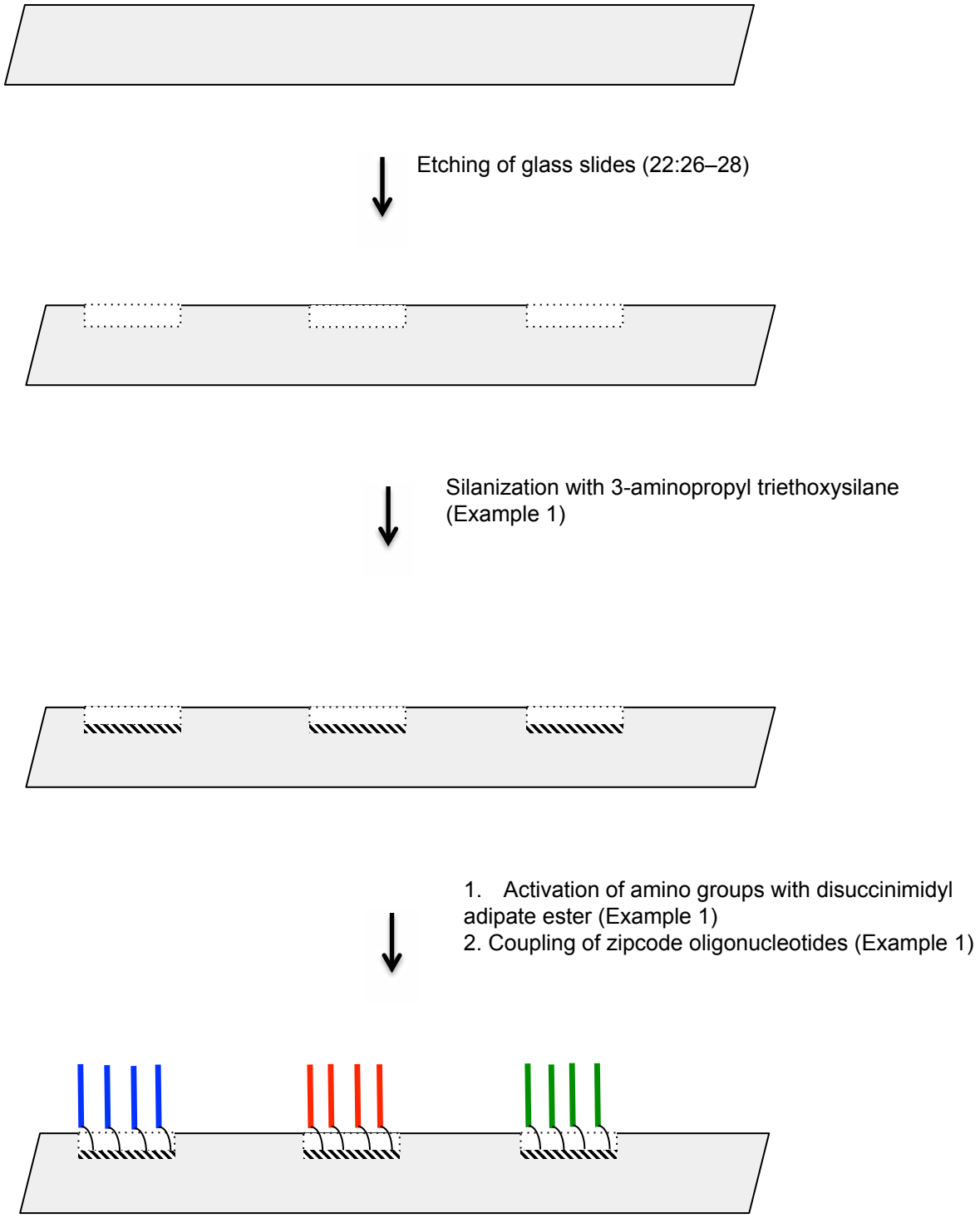
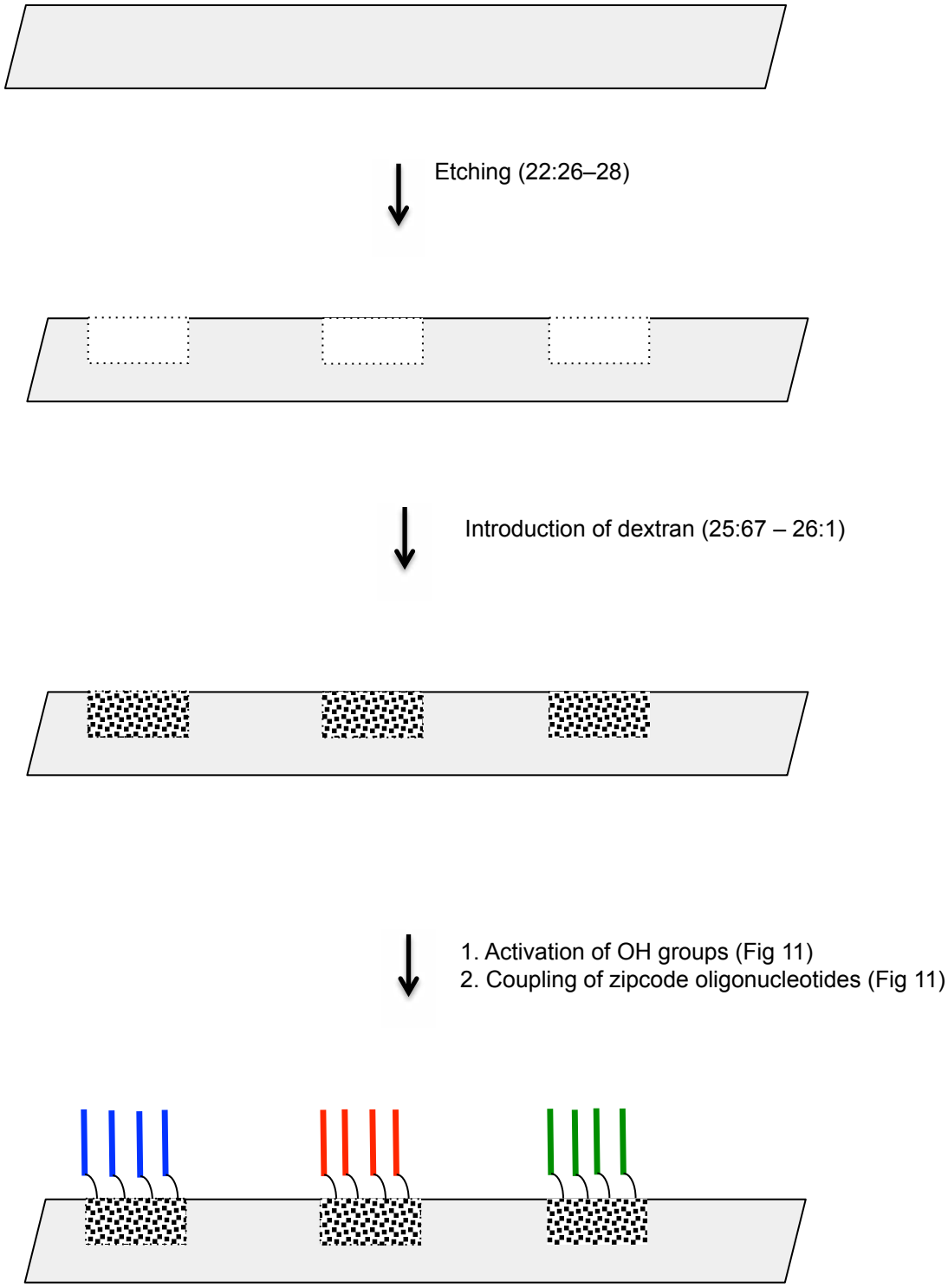

Etching of glass slides (22:26–28)
Silanization with 3-aminopropyl triethoxysilane (Example 1)
1. Activation of amino groups with disuccinimidyl adipate ester (Example 1)
2. Coupling of zipcode oligonucleotides (Example 1)

Figure 5


Etching (22:26–28)
Introduction of dextran (25:67 – 26:1)
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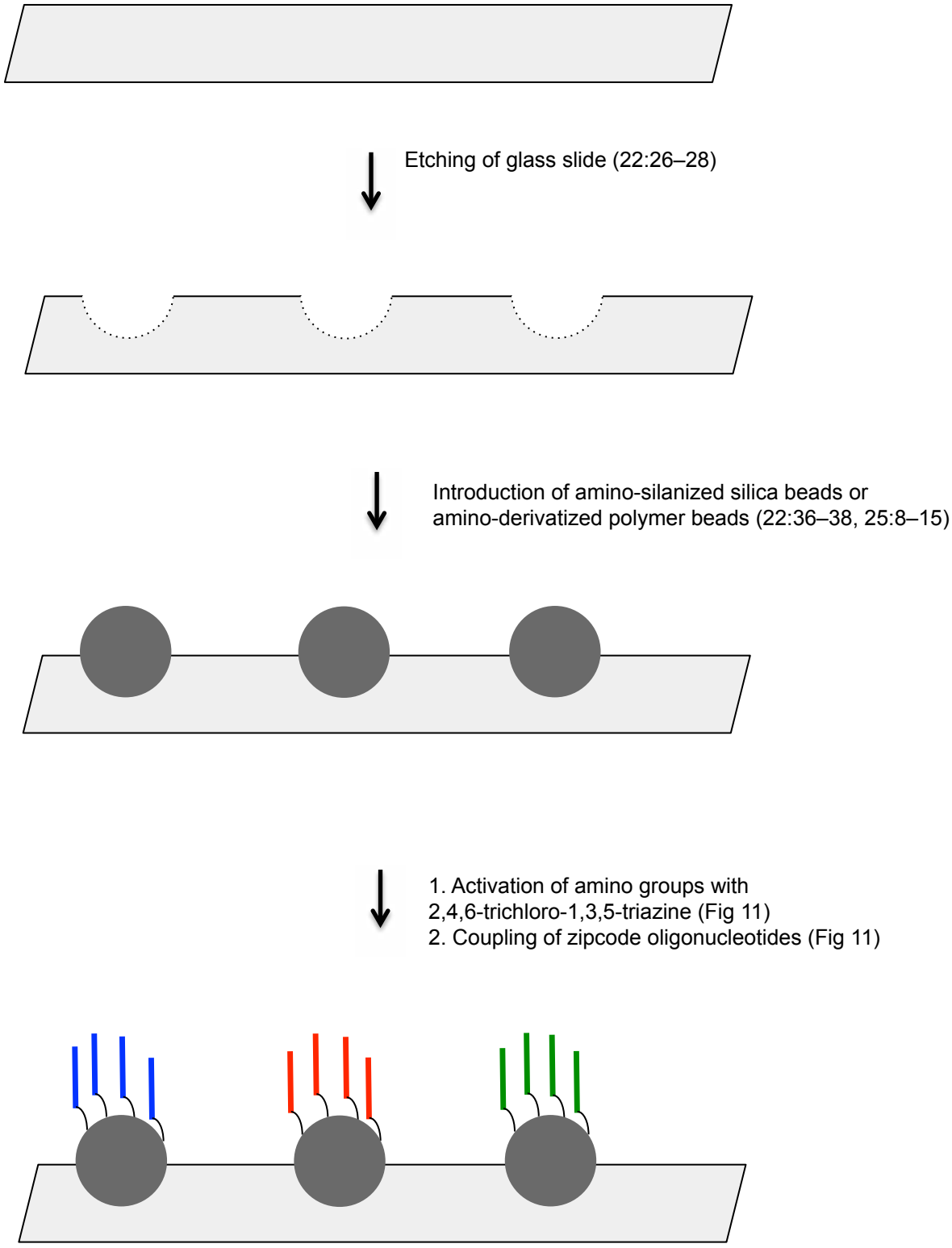
Etching of glass slide (22:26–28)
Introduction of amino-silanized silica beads or
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Date May 27, 2016 at 10:19 AM

Dear Maria,

Your figures are beautiful.

Kindly look at the enclosed v02 powerpoint. I have labeled the figures 5A, 5B, 5C etc. so we are all talking about the same thing.

1. If you look in the patent, we got nice results from example 6. Is example 6 covered in 5A, 5B, or 5C? If not, kindly include a version for Example 6…

2. Starting with your Figure 5G, I made a new version (Figure 5H) that allows for the oligo to be attached to the bead FIRST, and then placed into the etched surface.

3. A slightly more detailed version of Figures 5G and 5H is illustrated in Figures 5I and 5J. Here I highlight that the silica or polystyrene bead is silanized to create a functionalized surface.

Maria — for your master figure, please verify that

Maria — for your master figure, please verify that Schemes “A”, “B”, and “C” are covered in the patent application — I think they nicely cover Figures 5A, 5B, and 5C. I really like the way you have played this out so nicely and logically.

"Scheme D" is beautiful and corresponds to Figures 5G and 5I.

Would you kindly include a "Scheme E”, which corresponds to Figures 5H and 5J?

Surface 4 —> Surface 4 with Zip Code Oligos + Etched Substrate —> Solid Support 4 with Zip Code Oligos

(When you show the 3 beads as "Surface 4 with Zip Code Oligos”, have the 3 blue, red, and green “oligos” on each of the 3 beads respectively…)

Notice that the last picture in Scheme E will be identical to the last picture in Scheme D. That’s the point!!

In terms of the movie, I don’t know how hard it is do do such a movie, but best would be to make a Movie that shows the processes for Schemes A, B, C, D, and E — since that way everyone can see the logical progression and equivalency of the Schemes D and E. If it is too much work, then just do Schemes D & E.

Maria, thank you again for all your hard work on this — would be great if you can send the revised Master Figure still today, but tomorrow will also work.

The movie can be sent on Monday or Tuesday…

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Markman_response_Figures_v02_MK_…

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US7083917_B2_Barany_1595_2006.pdf

ATT00002.htm

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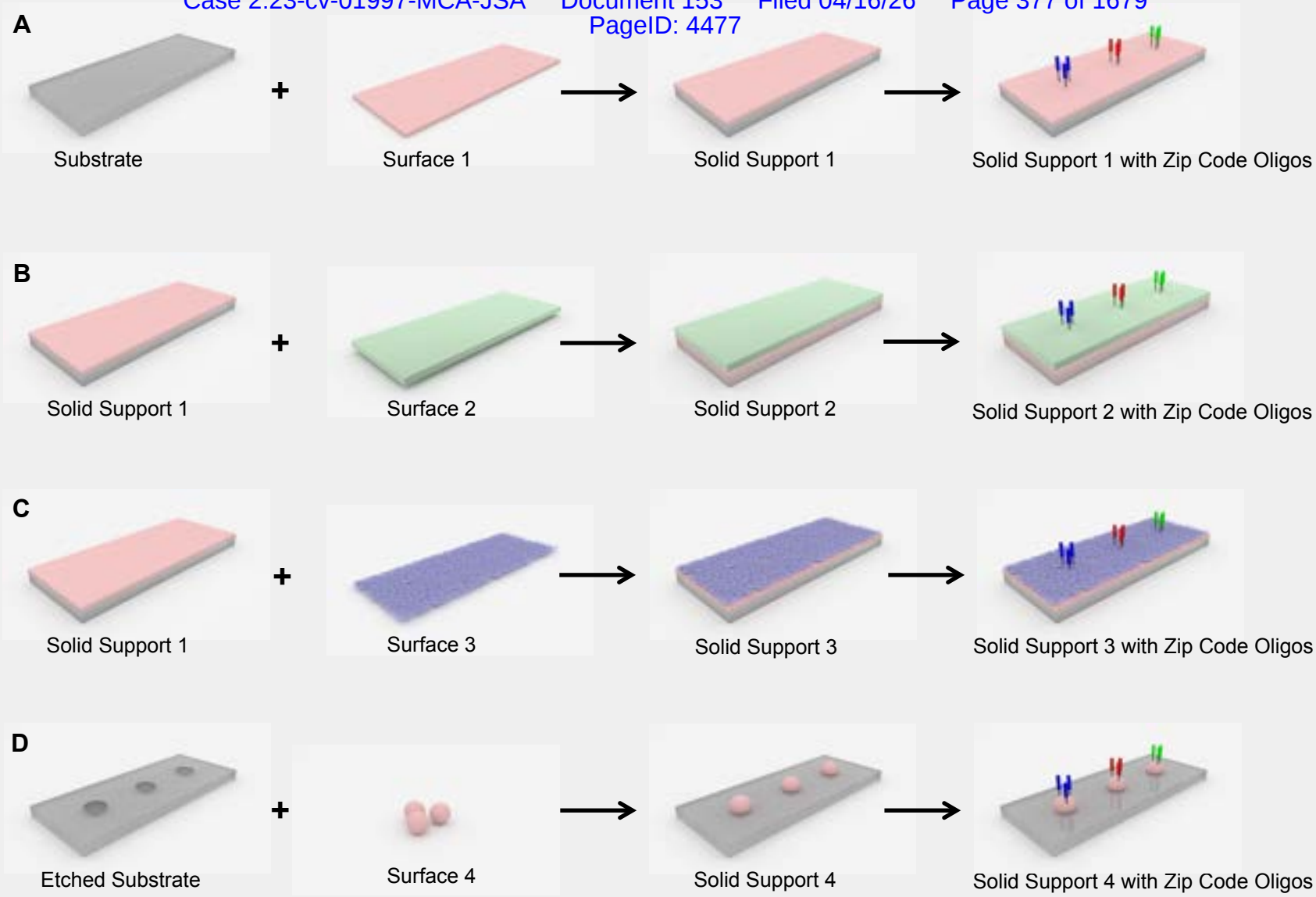
A
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For the Master Figure, just need to add a “Scheme E” — you already have all the “parts”, should be straightforward.

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ATT00001.htm

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work today…

Thanks a million for all your help,

Francis

[redacted]

On May 27, 2016, at 8:26 AM, Maria Kempe <maria.kempe@med.lu.se> wrote:

Dear All,

Please find attached the pdf of the Francis-slides that I sent yesterday.

Please also find attached a new figure along the theme "substrate + surface –> solid support –> solid support with zip code oligos". Please let me know if the combinations in the figure are ok. We can also change the colors, texture (glossy, transparent) etc... Please let me know what you want. My idea is to have Henrik make a movie of figure D.

All the best,
Maria

From: Francis Barany [barany@med.cornell.edu]
Sent: Thursday, May 26, 2016 9:05 PM
To: Maria Kempe
Cc: Pearson, Matthew; George Barany; Robert Hammer; Monib Zirvi; Valerie Cross; Matthew Lubin; Brian Kelly
Subject: Re: Confidential Status Report regarding Cornell University, et al. v. Illumina

Dear Maria,

Looks great but my iPhone is distorting the figures. Would you kinds email to all of us also as a PDF?

Looking forward to your ABC pictures later tonight, please send as BOTH Pptx and PDF

please send as BOTH ppt x and PDF.

Your work on all this is terrific!

Best,

Francis

Sent from my iPhone

On May 26, 2016, at 3:00 PM, Maria Kempe <maria.kempe@med.lu.se> wrote:

Dear All,

I am sending some suggestions for Francis slides with this email. My A-B-C-picture will come later tonight. Some more photos will come tomorrow.

Best regards,
Maria

From: Pearson, Matthew [mpearson@AKINGUMP.com]
Sent: Thursday, May 26, 2016 4:45 PM
To: Francis Barany; Maria Kempe
Cc: George Barany; Robert Hammer; Monib Zirvi; Valerie Cross; Matthew Lubin; Brian Kelly
Subject: RE: Confidential Status Report regarding Cornell University, et al. v. Illumina

I agree – the pictures look great

Thanks, everyone, for your thoughts and work on this.

From: Francis Barany [mailto:barany@med.cornell.edu]
Sent: Wednesday, May 25, 2016 3:21 PM
To: Maria Kempe
Cc: Pearson, Matthew; George Barany; Robert Hammer; Monib Zirvi; Valerie Cross; Matthew Lubin; Brian Kelly
Subject: Re: Confidential Status Report regarding Cornell University, et al. v. Illumina
Importance: High

Dear Maria,

Very creative! I'm hungry!

I defer to Matthew P.'s thoughts on how best to use these photos, and when it will have the greatest impact.

Yes, Fig. 1B looks correct as the final part of the process. Would you please send the powerpoint of the figure as I suggested, with Example A, B, and C, and the steps of combining substrate (glass in all cases, but Example 1B has dimples) with surface (polyethylene plate, silica beads, polymer), to create the solid support? Would you also please send the more complete powerpoint which includes the oligonucleotides?

When you get a chance, kindly label my slides 5 & 6 accordingly (glass, polymer — chemistry), etc.

Maria, the pictures are great, now we need to back it up to teach the judge that polymer = chemistry, and silica bead = chemistry.

With regards to the movie, please call my office and we can discuss...

Thanks!

Francis

[redacted]

We need to decide exactly which scenario we should show in the movie. So let's think about it...

Maria

On May 25, 2016, at 2:33 PM, Maria Kempe

<maria.kempe@med.lu.se> wrote:

Dear All,

Please find attached some attempts to visualize one of the Cornell approaches vs the Illumina approach. Please also find a figure showing a slide with beads and oligos (for revision of Fig. 1B of my previously submitted comments). The latter figure was done by my brother Henrik. Please let me know if this is what you have in mind as the final product of Fig 1B. We can change it otherwise. Henrik can make a movie along these lines.

Best regards,
Maria

From: Francis Barany [barany@med.cornell.edu]
Sent: Wednesday, May 25, 2016 3:57 PM
To: Pearson, Matthew; Maria Kempe; George Barany; Robert Hammer
Cc: Monib Zirvi; Valerie Cross; Matthew Lubin; Brian Kelly; Francis Barany
Subject: Re: Confidential Status Report regarding Cornell University, et al. v. Illumina

Dear Bob, George, and Maria,

Just spoke with Bob. He reminded me that Maria should point out that use of glass, polystyrene, or silica beads are just another form of the "surface".

He suggested labeling what "chemistry" the bead is made of — i.e. technically it is no different than our polymer surfaces. (See enclosed paper to see what chemistry Illumina is using, e.g. Silica — pg 875, I've also copied it for you below).

(Matthew P. — have they changed their bead chemistry to polystyrene? Independent of what their bead is made of, it is still the "surface", i.e. it has chemistry

Illumina is trying to argue that their glass wells are a first solid support, and the beads are a second solid support (not covalently attached). The oligo is attached covalently to a linker — but they claim the

bead is a physical object, not a chemical.

What we need to explain is that in both cases the substrate is glass, the surface is chemistry. The surface can be either attached via covalent bonds to the substrate, or adsorbed to the substrate. The linker is chemistry that is part of the surface. The linker-surface can also be either attached via covalent bonds to the substrate, or adsorbed to the substrate. The oligonucleotide is then covalently attached to the linker.

(Maria, see Fig. 2B in the attached as an example of how the beads look when buried into the fiber-optic wells — you may use this as a guide for your drawing of "Example B")

Hope this clarifies…

Best,

Francis

[redacted]

Preparation of Oligonucleotide-Linked Beads and Bead Pools

A set of 1536 universal capture oligonucleotide sequences was synthesized. Each sequence was individually immobilized on activated beads, as follows, to create 1536 bead types. Silica beads ~3 µm in diameter (Bangs Laboratories, Inc.) were amino functionalized by incubation in 2.5% 3-amino-propyl-trimethoxysilane (Aldrich) in ethanol for 1 h at RT and then activated by reaction with 2% 2,4,6-trichloro-1,3,5-triazine (Aldrich) in acetonitrile for 2 h at room temperature. Synthetic oligonucleotides labeled at the 5 terminus with a primary amine were covalently attached to the activated beads by overnight reaction at 50°C in a solution of 3 M NaCl and 100 mM sodium

carbonate (pH 11). All reagents were of highest purity grade. Empirical measurements indicated that, on average, each bead carried on the order of 106 oligonucleotides. Following quality assessment, 16 of the bead types were discarded due to low signal-to-noise ratios. The remaining bead types were combined to create a pool containing 1520 functional bead types, each representing a unique capture sequence. The sequences were designed to serve as noninteracting decodable address sequences in addition to their function as probes that capture assay products from solution. They were selected to be 22 to 24 bases long with minimal crosscomplementarity, similar GC content and Tm, no runs of a single base longer than five, and low similarity to human genomic sequences.

<Cornell approach.jpg><Illumina approach.jpg>
<Slide with beads & oligos.jpg>

The information contained in this e-mail message is intended only for the personal and confidential use of

the recipient(s) named above. If you have received this communication in error, please notify us immediately by e-mail, and delete the original message.
<MK 160526 Markman_response_Figures_v01-1.pptx>
<MK 160526 Markman_response_Figures_v01-1.pdf>
<Figure.jpg>

<Figure.pdf>

View less

Subject Re: Confidential Status Report regarding Cornell University, et al. v. Illumina

From Francis Barany <barany@med.cornell.edu>

To: Maria Kempe <maria.kempe@med.lu.se>

Cc: Pearson, Matthew <mpearson@AKINGUMP.com>, George Barany <barany@umn.edu>, Robert Hammer <rphammer@gmail.com>, Monib Zirvi <matzirvi@yahoo.com>, Valerie Cross <vlc1@cornell.edu>, Matthew Lubin <lubingenetics@me.com>, Brian Kelly <bjk44@cornell.edu>

Date May 27, 2016 at 10:42 AM

Dear Maria,

Wow, a new graphic card…

This master figure is absolutely professional grade!

I think you will see that making Scheme E just requires re-arranging parts from Scheme D, since they are equivalent, just the order of adding the oligo is different. Hopefully, it won't take that long...

Again, please thank Henrik, and no worries if it is only finished tomorrow.

Best,

Francis

[redacted]

On May 27, 2016, at 10:34 AM, Maria Kempe
<maria.kempe@med.lu.se> wrote:

Dear Francis, message received. I will see how far we get today. The master figures take some time to do. We bought a new graphic card for the computer yesterday to give the computer some more muscles in order to speed up the calculations, but still it takes some time...
Maria

View more

Subject RE: Confidential Status Report regarding Cornell University, et al. v. Illumina

From Maria Kempe <maria.kempe@med.lu.se>

To: Francis Barany <barany@med.cornell.edu>

Cc: Pearson, Matthew <mpearson@AKINGUMP.com>, George Barany <barany@umn.edu>, Robert Hammer <rphammer@gmail.com>, Monib Zirvi <matzirvi@yahoo.com>, Valerie Cross <vlc1@cornell.edu>, Matthew Lubin <lubingenetics@me.com>, Brian Kelly <bjk44@cornell.edu>

Date May 27, 2016 at 11:04 AM

Dear All,

Example 6 does not specify the exact monomers (leaving us more room to choose freely) while Examples 11–13 are very specific and even gives the catalogue # of the monomers. My slide figures 5 are restricted to the catalogue monomers. I will do some more figures using this extra room.

George and Bob: as I see it, we can choose any PEG-containing cross-linker (for example dimethacrylate-PEGs of any length) and any length of of PEG in PEG-acrylates since Example 6 does not specify the length. At my deposition, the lawyer was concerned about the length of the PEG and he had me circle the PEG-portion of Fig 32 (which is the catalogue monomer from Example 11 and 13, which is a quite short PEG). I got the impression that he wanted our PEG to be as short as possible. BUT - Fig 11 says that n can be 6-200 (==> MW 244-8810) and Example 6 does not restrict the length of PEG. So my question is: what length should we choose for the figure?

Maria

From: Francis Barany [barany@med.cornell.edu]

Sent: Friday, May 27, 2016 4:19 PM

To: Maria Kempe

Cc: Pearson, Matthew; George Barany; Robert Hammer; Monib Zirvi;

Cc: Pearson, Matthew; George Barany; Robert Hammer; Mohib Zihvi; Valerie Cross; Matthew Lubin; Brian Kelly; Francis Barany
Subject: Re: Confidential Status Report regarding Cornell University, et al. v. Illumina

Dear Maria,

Your figures are beautiful.

Kindly look at the enclosed v02 powerpoint. I have labeled the figures 5A, 5B, 5C etc. so we are all talking about the same thing.

1. If you look in the patent, we got nice results from example 6. Is example 6 covered in 5A, 5B, or 5C? If not, kindly include a version for Example 6…

2. Starting with your Figure 5G, I made a new version (Figure 5H) that allows for the oligo to be attached to the bead FIRST, and then placed into the etched surface.

3. A slightly more detailed version of Figures 5G and 5H is illustrated in Figures 5I and 5J. Here I highlight that the silica or polystyrene bead is silanized to create a functionalized surface.

Maria — for your master figure, please verify that Schemes “A”, “B”, and “C” are covered in the patent application — I think they nicely cover Figures 5A, 5B, and 5C. I really like the way you have played this out so nicely and logically.

"Scheme D" is beautiful and corresponds to Figures 5G and 5I.

Would you kindly include a "Scheme E”, which corresponds to Figures 5H and 5J?

Surface 4 —> Surface 4 with Zip Code Oligos + Etched Substrate —> Solid Support 4 with Zip Code Oligos

(When you show the 3 beads as "Surface 4 with Zip Code Oligos”, have the 3 blue, red, and green “oligos” on each of the 3 beads respectively…)

Notice that the last picture in Scheme E will be identical

to the last picture in Scheme D. That's the point!!

In terms of the movie, I don't know how hard it is do do such a movie, but best would be to make a Movie that shows the processes for Schemes A, B, C, D, and E — since that way everyone can see the logical progression and equivalency of the Schemes D and E. If it is too much work, then just do Schemes D & E.

Maria, thank you again for all your hard work on this — would be great if you can send the revised Master Figure still today, but tomorrow will also work.

The movie can be sent on Monday or Tuesday…

Maria — please send me an email to verify that you received this...

All the best,

Francis

[redacted]

View less

Subject RE: Confidential Status Report regarding Cornell University, et al. v. Illumina

From Maria Kempe <maria.kempe@med.lu.se>

To: Francis Barany <barany@med.cornell.edu>

Cc: Pearson, Matthew <mpearson@AKINGUMP.com>, George Barany <barany@umn.edu>, Robert Hammer <rphammer@gmail.com>, Monib Zirvi <matzirvi@yahoo.com>, Valerie Cross <vlc1@cornell.edu>, Matthew Lubin <lubingenetics@me.com>, Brian Kelly <bjk44@cornell.edu>

Date May 27, 2016 at 11:14 AM

Just a question:

should it be zip-code, zip code, or zipcode?

From: Francis Barany [barany@med.cornell.edu]
Sent: Friday, May 27, 2016 4:19 PM
To: Maria Kempe
Cc: Pearson, Matthew; George Barany; Robert Hammer; Monib Zirvi; Valerie Cross; Matthew Lubin; Brian Kelly; Francis Barany
Subject: Re: Confidential Status Report regarding Cornell University, et al. v. Illumina

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View less

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Date May 27, 2016 at 11:19 AM

Dear Maria,

In the patent we say “zip code”.

I am answering your other question right now, please be patient…

Francis

[redacted]

> On May 27, 2016, at 11:14 AM, Maria Kempe <maria.kempe@med.lu.se> wrote:
>
> Just a question:
>
> should it be zip-code, zip code, or zipcode?
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Etched Substrate —> Solid Support 4 with Zip Code Oligos

(When you show the 3 beads as "Surface 4 with Zip

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All the best,

Francis

[redacted]

View less

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From Francis Barany <barany@med.cornell.edu>

To: Maria Kempe <maria.kempe@med.lu.se>

Cc: Pearson, Matthew <mpearson@AKINGUMP.com>, George Barany <barany@umn.edu>, Robert Hammer <rphammer@gmail.com>, Monib Zirvi <matzirvi@yahoo.com>, Valerie Cross <vlc1@cornell.edu>, Matthew Lubin <lubingenetics@me.com>, Brian Kelly <bjk44@cornell.edu>, Francis Barany <barany@med.cornell.edu>

Date May 27, 2016 at 11:38 AM

Dear Maria,

Briefly, the lawyer was stetting a trap for you and others (which became clearer when he took out of context comments that each of us made during our individual deposition — Monib was also at the Markman hearing) — I prefer that Matthew handle any further communication about depositions privately with you or other inventors…

Let me try to directly answer your question. In the figure put “n” and say n = 6 to 200.

Briefly, our position is that the surface and linker are covalently connected, and are as one. This is independent of whether the surface is in the form of beads, a flat surface, a 3-Dimensional polymer, polymer that fills etched areas on the substrate, etc. The oligonucleotide is covalently attached to the surface, and again, that may occur prior to putting the surface (i.e. beads) on the substrate to create

the solid support, or after putting the surface on the substrate to create the solid support (i.e. spotting the oligos)

oligos).

In the patent we describe:

“The linker molecules can be attached to the substrate via carbon--carbon bonds using, for example, (poly)tri-fluorochloroethylene surfaces or, preferably, by siloxane bonds (using, for example, glass or silicon oxide surfaces). Siloxane bonds with the surface of the substrate may be formed in one embodiment via reactions of linker molecules bearing trichlorosilyl groups. The linker molecules may optionally be attached in an ordered array, i.e., as parts of the head groups in a polymerized monolayer. In alternative embodiments, the linker molecules are adsorbed to the surface of the substrate. "

Our position is that the bead is just an extended surface which is covalently attached to the linker — and then oligo. When the individual beads sit in the wells, they are simply an extension of "the linker molecules adsorbed to the surface of the substrate."

Hope this helps,

Francis

[redacted]

P.S. from Wikipedia — and pertaining to Bob’s comments:

Plywood is a sheet material manufactured from thin layers or "plies" of wood veneer that are glued together

with adjacent layers having their wood grain rotated up to 90 degrees to one another. It is an engineered wood from the family of manufactured boards which includes medium-density fibreboard(MDF) and particle board (chipboard).

All plywoods bind resin and wood fibre sheets (cellulose cells are long, strong and thin) to form a composite material.

https://en.wikipedia.org/wiki/Plywood

A composite material (also called a composition material or shortened to composite) is a material made from two or more constituent materials with significantly different physical or chemical properties that, when combined, produce a material with characteristics different from the individual components. The individual components remain separate and distinct within the finished structure.

https://en.wikipedia.org/wiki/Composite_material

On May 27, 2016, at 11:04 AM, Maria Kempe <maria.kempe@med.lu.se> wrote:

Dear All,

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[redacted]

View less

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Date May 27, 2016 at 2:55 PM

Dear All,

Please find attached the revised Master Figure A-E. Let me know if it is ok or if it should be adjusted somehow.

A is covered by Example 1.

B is covered by Example 9–13 + Figure 11.

C is covered by Example 1 or 9 (or any other silanization) + any of the following:
(i) introduction of dextran according to 25:67–26:6 (Cass et al.) or
(ii) grafting with polymer network according to 25:8–15 or
(iii) adsorption of fibronectin according to Example 1 (Jönsson et al.) or
(iv) grafting of PEG according to 23:5 and Figure 11 or
(v) attachment of carbohydrates according to 23:7

Henrik is rendering the first movie now (according to D). It will take 31 h if everything goes well. The computer speed is the limiting factor. Parts of the D-movie can be used for the E-movie, so that one will probably be a little quicker. Hopefully we can have two movies ready by Tuesday. The others can be done later, but due to the long rendering times they will probably not be finished by Tuesday. So far of what I have

seen, it looks great - even better than the master figures.

I will update the Francis-slides with the different PEG-lengths

later today or tomorrow.

All the best,
Maria

From: Francis Barany [barany@med.cornell.edu]
Sent: Friday, May 27, 2016 4:19 PM
To: Maria Kempe
Cc: Pearson, Matthew; George Barany; Robert Hammer; Monib Zirvi; Valerie Cross; Matthew Lubin; Brian Kelly; Francis Barany
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From Maria Kempe <maria.kempe@med.lu.se>

To: Francis Barany <barany@med.cornell.edu>

Cc: Pearson, Matthew <mpearson@AKINGUMP.com>, George Barany <barany@umn.edu>, Robert Hammer <rphammer@gmail.com>, Monib Zirvi <matzirvi@yahoo.com>, Valerie Cross <vlc1@cornell.edu>, Matthew Lubin <lubingenetics@me.com>, Brian Kelly <bjk44@cornell.edu>

Date May 27, 2016 at 2:58 PM

Forgot to attach - here it is!

From: Maria Kempe
Sent: Friday, May 27, 2016 8:55 PM
To: Francis Barany
Cc: Pearson, Matthew; George Barany; Robert Hammer; Monib Zirvi; Valerie Cross; Matthew Lubin; Brian Kelly
Subject: RE: Confidential Status Report regarding Cornell University, et al. v. Illumina

Dear All,

Please find attached the revised Master Figure A-E. Let me know if it is ok or if it should be adjusted somehow.

A is covered by Example 1.

B is covered by Example 9–13 + Figure 11.

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or
(ii) grafting with polymer network according to 25:8–15 or
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et al.) or
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I will update the Francis-slides with the different PEG-lengths later today or tomorrow.

All the best,
Maria

From: Francis Barany [barany@med.cornell.edu]
Sent: Friday, May 27, 2016 4:19 PM
To: Maria Kempe
Cc: Pearson, Matthew; George Barany; Robert Hammer; Monib Zirvi; Valerie Cross; Matthew Lubin; Brian Kelly; Francis Barany
Subject: Re: Confidential Status Report regarding Cornell University, et al. v. Illumina

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Would you kindly include a "Scheme E”, which corresponds to Figures 5H and 5J?

Surface 4 —> Surface 4 with Zip Code Oligos + Etched Substrate —> Solid Support 4 with Zip Code Oligos

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[redacted]

[redacted]

View less

Master Figure A-E.pdf

Subject Re: Confidential Status Report regarding Cornell University, et al. v. Illumina

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Date May 27, 2016 at 3:02 PM

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Francis

[redacted]

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Date May 27, 2016 at 3:18 PM

Dear Francis,

I forgot to attach in the first mail, but sent a second one a minute later. Anyway, here it comes again. I also did a short-version (attached). The pdf's do not work well - too low resolution. I will try to increase the resolution or send it in another format.

Maria

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Francis

[redacted]

View less

Master Figure A-E.pdf

Master Figure Short-version.pdf

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Date May 27, 2016 at 3:32 PM

I received error messages saying that the message was too big to send to George, Bob, and Matthew L.
Francis and Matthew P: did you receive it?

I need to figure out how to get the files to you. Do you use drop box? Icloud?

Maria

From: Francis Barany [barany@med.cornell.edu]
Sent: Friday, May 27, 2016 9:01 PM
To: Maria Kempe
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Francis

[redacted]
barany@med.cornell.edu

[redacted]

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Cc: Pearson, Matthew; George Barany; Robert Hammer; Monib

Zirvi; Valerie Cross; Matthew Lubin; Brian Kelly; Francis Barany
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View less

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Date May 27, 2016 at 3:37 PM

I will send them as zip files (in separate mails). Please let me know if you receive them.

Maria

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Sent: Friday, May 27, 2016 9:01 PM
To: Maria Kempe
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Master Figure A-E.pdf.zip

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Cc: Pearson, Matthew <mpearson@AKINGUMP.com>, George Barany <barany@umn.edu>, Robert Hammer <rphammer@gmail.com>, Monib Zirvi <matzirvi@yahoo.com>, Valerie Cross <vlc1@cornell.edu>, Matthew Lubin <lubingenetics@me.com>, Brian Kelly <bjk44@cornell.edu>

Date May 27, 2016 at 3:41 PM

From: Francis Barany [barany@med.cornell.edu]
Sent: Friday, May 27, 2016 9:01 PM
To: Maria Kempe
Cc: Pearson, Matthew; George Barany; Robert Hammer; Monib Zirvi; Valerie Cross; Matthew Lubin; Brian Kelly
Subject: Re: Confidential Status Report regarding Cornell University, et al. v. Illumina

Dear Maria,

Sorry, I did not see an attachment, would you kindly resend with the attachment in pdf and jpg?

Thanks!

Francis

[redacted]

barany@med.cornell.edu

[redacted]

[redacted]

On May 27, 2016, at 2:55 PM, Maria Kempe <maria.kempe@med.lu.se> wrote:

Dear All,

Please find attached the revised Master Figure A-E. Let me know if it is ok or if it should be adjusted somehow.

A is covered by Example 1.

B is covered by Example 9–13 + Figure 11.

C is covered by Example 1 or 9 (or any other silanization) + any of the following:
(i) introduction of dextran according to 25:67–26:6 (Cass et al.) or
(ii) grafting with polymer network according to 25:8–15 or
(iii) adsorption of fibronectin according to Example 1 (Jönsson et al.) or
(iv) grafting of PEG according to 23:5 and Figure 11 or
(v) attachment of carbohydrates according to 23:7

Henrik is rendering the first movie now (according to D). It will take 31 h if everything goes well. The computer speed is the limiting factor. Parts of the D-movie can be used for the E-movie, so that one will probably be a little quicker. Hopefully we can have two movies ready by Tuesday. The others can be done later, but due to the long rendering times they will probably not be finished by Tuesday. So far of what I have seen, it looks great - even better than the master figures.

I will update the Francis-slides with the different PEG-lengths later today or tomorrow.

All the best,
Maria

From: Francis Barany [barany@med.cornell.edu]

Sent: Friday, May 27, 2016 4:19 PM

To: Maria Kempe

Cc: Pearson, Matthew; George Barany; Robert Hammer; Monib Zirvi; Valerie Cross; Matthew Lubin; Brian Kelly; Francis Barany

Subject: Re: Confidential Status Report regarding Cornell University, et al. v. Illumina

Dear Maria,

Your figures are beautiful.

Kindly look at the enclosed v02 powerpoint. I have labeled the figures 5A, 5B, 5C etc. so we are all talking about the same thing.

1. If you look in the patent, we got nice results from example 6. Is example 6 covered in 5A, 5B, or 5C? If not, kindly include a version for Example 6…

2. Starting with your Figure 5G, I made a new version (Figure 5H) that allows for the oligo to be attached to the bead FIRST, and then placed into the etched surface.

3. A slightly more detailed version of Figures 5G and 5H is illustrated in Figures 5I and 5J. Here I highlight that the silica or polystyrene bead is silanized to create a functionalized surface.

Maria — for your master figure, please verify that Schemes “A”, “B”, and “C” are covered in the patent application — I think they nicely cover Figures 5A, 5B, and 5C. I really like the way you have played this out so nicely and logically.

"Scheme D" is beautiful and corresponds to Figures 5G and 5I.

Would you kindly include a "Scheme E”, which corresponds to Figures 5H and 5J?

Surface 4 —> Surface 4 with Zip Code Oligos + Etched Substrate —> Solid Support 4 with Zip Code Oligos

(When you show the 3 beads as "Surface 4 with Zip Code Oligos”, have the 3 blue, red, and green “oligos” on each of the 3 beads respectively…)

Notice that the last picture in Scheme E will be identical to the last picture in Scheme D. That’s the point!!

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Maria, thank you again for all your hard work on this — would be great if you can send the revised Master Figure still today, but tomorrow will also work.

The movie can be sent on Monday or Tuesday…

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All the best,

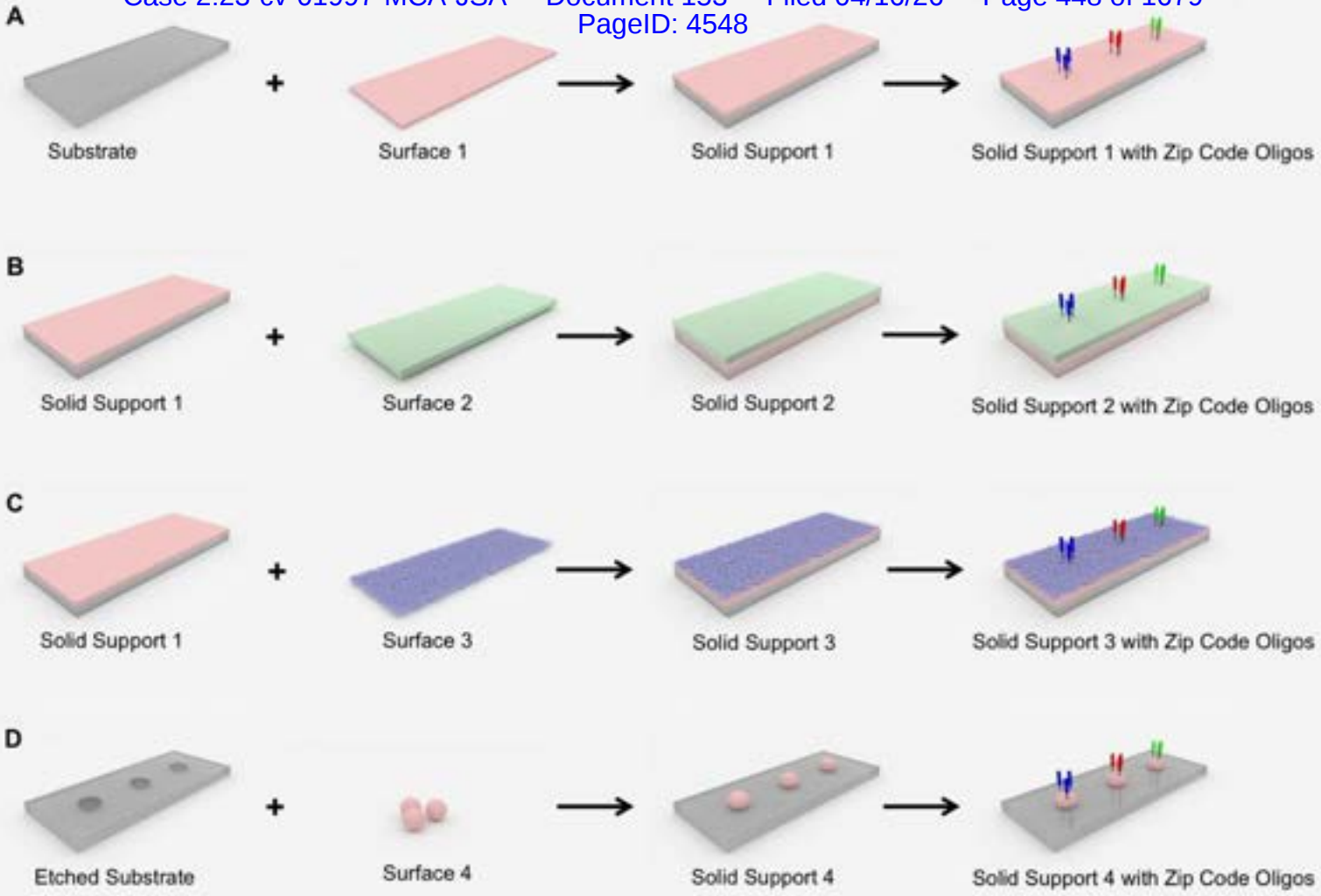
Francis

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

View less

Master Figure Short-version.jpg.zip


A
Substrate
Surface 1
Solid Support 1
Solid Support 1 with Zip Code Oligos
B
Solid Support 1
Surface 2
Solid Support 2
Solid Support 2 with Zip Code Oligos
C
Solid Support 1
Surface 3
Solid Support 3
Solid Support 3 with Zip Code Oligos
D
Etched Substrate
Surface 4
Solid Support 4
Solid Support 4 with Zip Code Oligos

Subject RE: Confidential Status Report regarding Cornell University, et al. v. Illumina

From Maria Kempe <maria.kempe@med.lu.se>

To: Francis Barany <barany@med.cornell.edu>

Cc: Pearson, Matthew <mpearson@AKINGUMP.com>, George Barany <barany@umn.edu>, Robert Hammer <rphammer@gmail.com>, Monib Zirvi <matzirvi@yahoo.com>, Valerie Cross <vlc1@cornell.edu>, Matthew Lubin <lubingenetics@me.com>, Brian Kelly <bjk44@cornell.edu>

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[redacted]

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Sent: Friday, May 27, 2016 4:19 PM

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Cc: Pearson, Matthew; George Barany; Robert Hammer; Monib Zirvi; Valerie Cross; Matthew Lubin; Brian Kelly; Francis Barany

Subject: Re: Confidential Status Report regarding Cornell University, et al. v. Illumina

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Francis

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

View less

Master Figure Short-version.pdf.zip

Subject Re: Confidential Status Report regarding Cornell University, et al. v. Illumina

From Francis Barany <barany@med.cornell.edu>

To: Maria Kempe <maria.kempe@med.lu.se>

Cc: Pearson, Matthew <mpearson@AKINGUMP.com>, George Barany <barany@umn.edu>, Robert Hammer <rphammer@gmail.com>, Monib Zirvi <matzirvi@yahoo.com>, Valerie Cross <vlc1@cornell.edu>, Matthew Lubin <lubingenetics@me.com>, Brian Kelly <bjk44@cornell.edu>

Date May 27, 2016 at 3:58 PM

Dear Maria,

PREFECT!

Got them all.

(And yes, I also use dropbox.)

Best,

Francis

[redacted]
barany@med.cornell.edu

[redacted]

> On May 27, 2016, at 3:40 PM, Maria Kempe <maria.kempe@med.lu.se> wrote:

From: Francis Barany [barany@med.cornell.edu]
Sent: Friday, May 27, 2016 9:01 PM
To: Maria Kempe
Cc: Pearson, Matthew; George Barany; Robert Hammer; Monib Zirvi; Valerie Cross; Matthew Lubin; Brian Kelly
Subject: Re: Confidential Status Report regarding Cornell University, et al. v. Illumina

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[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

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All the best,
Maria

From: Francis Barany [barany@med.cornell.edu]
Sent: Friday, May 27, 2016 4:19 PM
To: Maria Kempe
Cc: Pearson, Matthew; George Barany; Robert Hammer; Monib Zirvi; Valerie Cross; Matthew Lubin; Brian Kelly; Francis Barany
Subject: Re: Confidential Status Report regarding Cornell University, et al. v. Illumina

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Maria — please send me an email to verify that you received this...

All the best,

Francis

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

<Master Figure Short-version.pdf.zip>

View less

Subject Privileged & Confidential: Memorial Weekend Summary re: Status Report regarding Cornell University, et al. v. Illumina, Part 2

From Francis Barany <barany@med.cornell.edu>

To: Pearson, Matthew <mpearson@akingump.com>, Valerie Cross <vlc1@cornell.edu>, George Barany <barany@umn.edu>, Robert Hammer <rphammer@gmail.com>, Monib Zirvi <matzirvi@yahoo.com>, Maria Kempe <maria.kempe@med.lu.se>, Matthew Lubin <lubingenetics@me.com>, Brian Kelly <bjk44@cornell.edu>

Date May 28, 2016 at 9:01 AM

Francis

[redacted]

barany@med.cornell.edu

[redacted]

A novel, high-performance random arra…

ATT00001.htm

Cass 1994.pdf

ATT00002.htm

Decoding_random_Zipcode_arrays_Gu…

ATT00003.htm

Gene Probe Assays on a Fibre-Optic Ev…

ATT00004.htm

Hedborg 1993.pdf

ATT00005.htm

Hyb_oligonucleotide_array_Guo_Smith…

ATT00006.htm

Subject Privileged & Confidential: Memorial Weekend Summary re: Status Report regarding Cornell University, et al. v. Illumina, Part 1

From Francis Barany <barany@med.cornell.edu>

To: Pearson, Matthew <mpearson@AKINGUMP.com>, Valerie Cross <vlc1@cornell.edu>, George Barany <barany@umn.edu>, Robert Hammer <rphammer@gmail.com>, Maria Kempe <maria.kempe@med.lu.se>, Monib Zirvi <matzirvi@yahoo.com>, Matthew Lubin <lubingenetics@me.com>, Brian Kelly <bjk44@cornell.edu>

Cc: Francis Barany <barany@med.cornell.edu>

Date May 28, 2016 at 9:02 AM

Dear Matthew P., Valerie, George, Bob, Maria, Monib, Matthew L., and Brian,

I thought it best to summarize all the comments and figures from the inventors in a powerpoint (also provided in pdf form).

I am also sending Maria's original comments, the report, Matthew P.'s comments to the inventors, and tiffs.

Next 2-3 emails will be relevant references.

Hope this helps you all to review the material one last time, and for Matthew to organize his response.

I will speak with Matthew Tuesday afternoon (time TBD) so if you have any additional comments / edits, please get them to us by Monday.

(Maria, we understand you and Henrik are making the two movies and these may take a bit longer…)

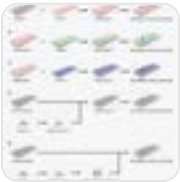
Matthew P., please let us know if there is anything else we should focus on or help with...

All the best,

Francis

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]



5-6-2016_Markman_CU v. Illumina-Rep…

ATT00001.htm

05-20-2016_Markman_Summary of R&…

ATT00002.htm

Markman_response_Figures_v03_MK_…

ATT00003.htm

Markman_response_Figures_v03_MK_…

ATT00004.htm

Kempe comments on Markman.doc

ATT00005.htm

Kempe comments on Markman.pdf

ATT00006.htm

ATT00007.htm

ATT00008.htm

Subject Privileged & Confidential: Memorial Weekend Summary re: Status Report regarding Cornell University, et al. v. Illumina, Part 3

From Francis Barany <barany@med.cornell.edu>

To: Pearson, Matthew <mpearson@AKINGUMP.com>, Valerie Cross <vlc1@cornell.edu>, George Barany <barany@umn.edu>, Robert Hammer <rphammer@gmail.com>, Maria Kempe <maria.kempe@med.lu.se>, Monib Zirvi <matzirvi@yahoo.com>, Matthew Lubin <lubingenetics@me.com>, Brian Kelly <bjk44@cornell.edu>

Cc: Francis Barany <barany@med.cornell.edu>

Date May 28, 2016 at 9:04 AM

Francis

[redacted]

barany@med.cornell.edu

[redacted]

Illumina Universal Bead Arrays_Fan_G…

ATT00001.htm

Jonsson 1982.pdf

ATT00002.htm

Kempe, Glad & Mosbach 1995.pdf

ATT00003.htm

Mandenius 1988.pdf

ATT00004.htm

Mosbach 1980.pdf

ATT00005.htm

Subject Privileged & Confidential: Memorial Weekend Summary re: Status Report regarding Cornell University, et al. v. Illumina, Part 4

From Francis Barany <barany@med.cornell.edu>

To: Pearson, Matthew <mpearson@AKINGUMP.com>, Valerie Cross <vlc1@cornell.edu>, George Barany <barany@umn.edu>, Robert Hammer <rphammer@gmail.com>, Maria Kempe <maria.kempe@med.lu.se>, Monib Zirvi <matzirvi@yahoo.com>, Matthew Lubin <lubingenetics@me.com>, Brian Kelly <bjk44@cornell.edu>

Cc: Francis Barany <barany@med.cornell.edu>

Date May 28, 2016 at 9:05 AM

Francis

[redacted]

barany@med.cornell.edu

[redacted]

US7122381B2_Kempe_2006.pdf

ATT00001.htm

Vágner_G_Barany_8194-9_PNAS_199…

ATT00002.htm

WO9305068A1_Kempe_1993.pdf

ATT00003.htm

Subject Re: Privileged & Confidential: Memorial Weekend Summary re: Status Report regarding Cornell University, et al. v. Illumina, Part 1

From Monib Zirvi <matzirvi@yahoo.com>

To: Francis Barany <barany@med.cornell.edu>

Cc: Pearson, Matthew <mpearson@AKINGUMP.com>, Valerie Cross <vlc1@cornell.edu>, George Barany <barany@umn.edu>, Robert Hammer <rphammer@gmail.com>, Maria Kempe <maria.kempe@med.lu.se>, Matthew Lubin <lubingenetics@me.com>, Brian Kelly <bjk44@cornell.edu>

Date May 28, 2016 at 9:19 AM

The figures look great. Focusing on the key examples and figures is most important to explain the issues.

Monib

Sent from my iPhone

On May 28, 2016, at 7:57 AM, Francis Barany <barany@med.cornell.edu> wrote:

> Dear Matthew P., Valerie, George, Bob, Maria, Monib, Matthew L., and Brian,
>
> I thought it best to summarize all the comments and figures from the inventors in a powerpoint (also provided in pdf form).
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barany@med.cornell.edu

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<5-6-2016_Markman_CU v. Illumina-Report & Recommendation.pdf>
<05-20-2016_Markman_Summary of R&R for Inventors.pdf>

<Markman_response_Figures_v03_MK_FB.pdf>
<Markman_response_Figures_v03_MK_FB.pptx>

<Kempe comments on Markman.doc>
<Kempe comments on Markman.pdf>

<Master Figure A-E_short.tiff>

<Master Figure A-E.tiff>

Subject RE: Privileged & Confidential: Memorial Weekend Summary re: Status Report regarding Cornell University, et al. v. Illumina, Part 1

From Maria Kempe <maria.kempe@med.lu.se>

To: Francis Barany <barany@med.cornell.edu>, Pearson, Matthew <mpearson@AKINGUMP.com>, Valerie Cross <vlc1@cornell.edu>, George Barany <barany@umn.edu>, Robert Hammer <rphammer@gmail.com>, Monib Zirvi <matzirvi@yahoo.com>, Matthew Lubin <lubingenetics@me.com>, Brian Kelly <bjk44@cornell.edu>

Date May 28, 2016 at 6:22 PM

Dear All,

Please find an updated version of the figures showing the different chemistries. 5K and 5L are new and are examples from Example 6. (I also fixed some typos on the other slides)

All the best,
Maria

From: Francis Barany [barany@med.cornell.edu]
Sent: Saturday, May 28, 2016 2:57 PM
To: Pearson, Matthew; Valerie Cross; George Barany; Robert Hammer; Maria Kempe; Monib Zirvi; Matthew Lubin; Brian Kelly
Cc: Francis Barany
Subject: Privileged & Confidential: Memorial Weekend Summary re: Status Report regarding Cornell University, et al. v. Illumina, Part 1

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[redacted]

View less

Markman_response_Figures_v02_MK_…

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To: Maria Kempe <Maria.Kempe@med.lu.se>, Pearson, Matthew <mpearson@AKINGUMP.com>, Valerie Cross <vlc1@cornell.edu>, George Barany <barany@umn.edu>, Robert Hammer <rphammer@gmail.com>, Monib Zirvi <matzirvi@yahoo.com>, Matthew Lubin <lubingenetics@me.com>, Brian Kelly <bjk44@cornell.edu>

Cc: Francis Barany <barany@med.cornell.edu>

Date May 28, 2016 at 8:18 PM

Dear Maria, Matthew P., Valerie, George, Bob, Monib, Matthew L., and Brian,

Sorry, just got back.

Maria, thank you again for the amazing job you are doing with all these figures.

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Matthew P., talk on Tuesday…

Best,

Francis

[redacted]

[redacted]

barany@med.cornell.edu

[redacted]

Markman_response_Figures_v04_MK_…

ATT00001.htm

Markman_response_Figures_v04_MK_…

ATT00002.htm

Subject RE: Privileged & Confidential: Memorial Weekend Summary re: Status Report regarding Cornell University, et al. v. Illumina, Part 1

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To: Francis Barany <barany@med.cornell.edu>, Pearson, Matthew <mpearson@AKINGUMP.com>, Valerie Cross <vlc1@cornell.edu>, George Barany <barany@umn.edu>, Robert Hammer <rphammer@gmail.com>, Monib Zirvi <matzirvi@yahoo.com>, Matthew Lubin <lubingenetics@me.com>, Brian Kelly <bjk44@cornell.edu>

Date May 29, 2016 at 4:24 AM

Dear All,

Henrik has finished the first movie. I will send it in a separate email. Henrik can save the movie in several different formats - this one is in mov format and is a little compressed. It works fine on my mac, running it with quicktime. Please verify that you can open it and run it on your computer. Another option is the mpg format - it works fine on Henrik's pc but does not work on my mac.

All the best,
Maria

From: Francis Barany [barany@med.cornell.edu]
Sent: Sunday, May 29, 2016 2:17 AM
To: Maria Kempe; Pearson, Matthew; Valerie Cross; George Barany; Robert Hammer; Monib Zirvi; Matthew Lubin; Brian Kelly
Cc: Francis Barany
Subject: Re: Privileged & Confidential: Memorial Weekend Summary re: Status Report regarding Cornell University, et al. v. Illumina, Part 1

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View less

Subject RE: Privileged & Confidential: Memorial Weekend Summary re: Status Report regarding Cornell University, et al. v. Illumina, Part 1

From Maria Kempe <maria.kempe@med.lu.se>

To: Francis Barany <barany@med.cornell.edu>, Pearson, Matthew <mpearson@AKINGUMP.com>, Valerie Cross <vlc1@cornell.edu>, George Barany <barany@umn.edu>, Robert Hammer <rphammer@gmail.com>, Monib Zirvi <matzirvi@yahoo.com>, Matthew Lubin <lubingenetics@me.com>, Brian Kelly <bjk44@cornell.edu>

Date May 29, 2016 at 4:25 AM

Here is the movie...

From: Francis Barany [barany@med.cornell.edu]
Sent: Sunday, May 29, 2016 2:17 AM
To: Maria Kempe; Pearson, Matthew; Valerie Cross; George Barany; Robert Hammer; Monib Zirvi; Matthew Lubin; Brian Kelly
Cc: Francis Barany
Subject: Re: Privileged & Confidential: Memorial Weekend Summary re: Status Report regarding Cornell University, et al. v. Illumina, Part 1

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Matthew P., talk on Tuesday

Matthew F., talk on Tuesday…

Best,

Francis

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

View less

TheFirstMovie.mov

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Date May 29, 2016 at 5:39 AM

Dear Maria,

The idea is to help the judge (and eventually, the jury) understand that Version D and Version E are equivalent.

Version D: In the first movie, we (a) drop all the beads into the wells at the same time, and then we (b) attach the oligos to the beads, one sequence (color) at a time.

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If I am not mistaken, this will also make it easier for Henrik to make the two movies...

I understand this takes a lot of computer time. I really appreciate that Henrik is spending all this time

helping the team. Again, we would prefer the two movies by the end of Tuesday, US Time, but if you still need to work on it Wednesday, then by the end

still need to work on it Wednesday, then by the end of Wednesday European time would still work for us…

Does this work for you and Henrik?

I will be speaking with Valerie and Matthew P. on Tuesday @ 2:00 PM EDT.

Thanks a million!

Francis

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Date May 29, 2016 at 5:40 AM

Would this work for the 2nd movie: a first sequence shows the attachment of the oligos to the beads (all at once) - the glass slide is not seen at this time - then a second sequence shows the glass slide and the oligo-beads come flying in from above, all at once?

Maria

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Date May 29, 2016 at 5:49 AM

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or

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Both versions will take the same computer time.

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Date May 29, 2016 at 6:05 AM

To make it similar to the first movie - maybe option 1 should chosen?

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Date May 29, 2016 at 8:41 AM

Could one of you please re-attach the current version of MOVIE 1 in a "reply all" to this e-mail? I have both a Mac and a PC and will view it on both formats before noon today. I am also available via e-mail, cell, and Skype for much of the day. GB

On Sun, May 29, 2016 at 5:04 AM, Maria Kempe <maria.kempe@med.lu.se> wrote:

> To make it similar to the first movie - maybe option 1 should chosen?
>
> ---
>
> **From:** Maria Kempe
> **Sent:** Sunday, May 29, 2016 11:49 AM
> **To:** Francis Barany
> **Cc:** Pearson, Matthew; Valerie Cross; George Barany; Robert Hammer; Monib Zirvi; Matthew Lubin; Brian Kelly
> **Subject:** RE: Privileged & Confidential: Memorial Weekend Summary re: Status Report regarding Cornell University, et al. v. Illumina, MOVIE 1
>
> For the 2nd movie - do you prefer:

1. we (a) attach the oligos to the beads, one sequence (color) at a time, and then we (b) drop all the beads into the wells at the same time.

or

2. we (a) attach the oligos to the beads, all sequences (color) at once, and then we (b) drop all the beads into the wells at the same time.

Both versions will take the same computer time.

Maria

Version E: In the second movie, we (a) attach the oligos to the beads, one sequence (color) at a time, and then we (b) drop all the beads into the wells at the same time.

If I am not mistaken, this will also make it easier for Henrik to make the two movies...

On May 29, 2016, at 5:22 AM, Maria Kempe <maria.kempe@med.lu.se> wrote:

Dear Francis,

Henrik and I discussed the issue of dropping all beads at the same time already yesterday and then realized that it would be better. However, to change it, takes another 8 hours on the computer and instead of stalling the rest of the movie I told Henrik to proceed with the one-at-one-dropping. It can be changed later, it just needs the 8 hours on the computer.

Henrik has already started with the second movie so I need to give him clear instruction on how it should be. I think the plan is to drop the pre-fabricated beads with oligos. I understand that you want the attachment of the oligos also included. I will check with him what he actually is doing!

Best regards,
Maria

From: Francis Barany [barany@med.cornell.edu]
Sent: Sunday, May 29, 2016 10:58 AM
To: Maria Kempe
Cc: Pearson, Matthew; Valerie Cross; George Barany; Robert Hammer; Monib Zirvi; Matthew Lubin; Brian Kelly; Francis Barany
Subject: Re: Privileged & Confidential: Memorial Weekend Summary re: Status Report regarding Cornell University, et al. v. Illumina, MOVIE 1

Dear Maria,

The movie is beautiful and worked great on my Mac using Quicktime. Saving in .mov works!

The detail and shadow work is fantastic!

I wanted to give you some immediate feedback before Henrik makes the second movie.

In this first movie, the beads are dropped into the etched wells one at a time. This is not the way it would be done. The beads (which lack oligos) would all be dropped into the wells at the same time. Would it be possible to make this simple edit to the first movie?

The oligo are attached one sequence (color) at a time. This is optional. One can attach oligo one at a time, or multiple oligos at a time. However, conceptually, it is easier for people to understand attaching one oligo at a time, so this part of the movie should stay unchanged.

For the second movie, I would suggest having the

beads off to the side in a straight row, and a little separated from each other. Then you add the oligos to the beads one sequence (color) at a time. Then drop all 3 beads into the wells at the same time.

Would that work for you?

Maria — again, thank you and Henrik for these terrific

Maria – again, thank you and Henrik for these terrific movies. I believe they will really help with the trial!

All the best,

Francis

[redacted]
barany@med.cornell.edu

[redacted]

On May 29, 2016, at 4:23 AM, Maria Kempe <maria.kempe@med.lu.se> wrote:

Dear All,

Henrik has finished the first movie. I will send it in a separate email. Henrik can save the movie in several different formats - this one is in mov format and is a little compressed. It works fine on my mac, running it with quicktime. Please verify that you can open it and run it on your computer. Another option is the mpg format - it works fine on Henrik's pc but does not work on my mac.

All the best,
Maria

From: Francis Barany [barany@med.cornell.edu]
Sent: Sunday, May 29, 2016 2:17 AM
To: Maria Kempe; Pearson, Matthew; Valerie Cross; George Barany; Robert Hammer; Monib Zirvi; Matthew Lubin; Brian Kelly
Cc: Francis Barany
Subject: Re: Privileged & Confidential: Memorial Weekend Summary re: Status Report regarding Cornell University, et al. v. Illumina, Part 1

Dear Maria, Matthew P., Valerie, George, Bob, Monib, Matthew L., and Brian,

Sorry, just got back.

Maria, thank you again for the amazing job you are doing with all these figures.

I have now placed your corrections into the master document, and sending out to all in pptx and pdf format.

Matthew P., talk on Tuesday…

Best,

Francis

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

View less

--
George Barany
Distinguished McKnight University Professor of Chemistry
University of Minnesota
Department of Chemistry
[redacted]

Subject Re: Privileged & Confidential: Memorial Weekend Summary re: Status Report regarding Cornell University, et al. v. Illumina, MOVIE 1

From Francis Barany <barany@med.cornell.edu>

To: Maria Kempe <maria.kempe@med.lu.se>, George Barany <barany@umn.edu>

Cc: Pearson, Matthew <mpearson@akingump.com>, Valerie Cross <vlc1@cornell.edu>, Robert Hammer <rphammer@gmail.com>, Monib Zirvi <matzirvi@yahoo.com>, Matthew Lubin <lubingenetics@me.com>, Brian Kelly <bjk44@cornell.edu>

Date May 29, 2016 at 9:23 AM

Dear Maria (and George),

Sorry, I fell back asleep.

1. GB, movie is attached again below. You can just click on it to run it. If you want to drag to you desktop, right click on the image, choose “view as icon”, hen drag the icon wherever you want. You need “Quicktime" on your computer.

2. Maria, please follow the following directions for the two movies, so they are as similar as possible.

Opening scene: We see the glass slide. We see the three cream-colored beads in a row, with some space between them (can be the same or different from the spacing when they are dropped onto the glass).

Movie 1 (Version D).

(i) We etch the three wells into the glass slide.

(ii) We drop all the beads into the wells at the

(ii) We drop all the beads into the wells at the same time.

(iii) We attach the oligos to the beads, one sequence (color) at a time.

Movie 2 (Version E).

(i) We etch the three wells into the glass slide.

(ii) We attach the oligos to the beads, one sequence (color) at a time.

(iii) We drop all the beads into the wells at the same time.

(Note, in both cases the 3 blue oligo strands simultaneously are attached to the first bead, then the 3 red oligo strands simultaneously are attached to the second bead, then the 3 green oligo strands simultaneously are attached to the third bead — you already have the movie this way, do not change.)

Hope this clarifies.

All the best,

Francis

[redacted]
barany@med.cornell.edu

[redacted]

TheFirstMovie_D1_05_29_2016.mov

ATT00001.htm

Subject RE: Privileged & Confidential: Memorial Weekend Summary re: Status Report regarding Cornell University, et al. v. Illumina, MOVIE 1

From Maria Kempe <maria.kempe@med.lu.se>

To: Francis Barany <barany@med.cornell.edu>, George Barany <barany@umn.edu>

Cc: Pearson, Matthew <mpearson@akingump.com>, Valerie Cross <vlc1@cornell.edu>, Robert Hammer <rphammer@gmail.com>, Monib Zirvi <matzirvi@yahoo.com>, Matthew Lubin <lubingenetics@me.com>, Brian Kelly <bjk44@cornell.edu>

Date May 29, 2016 at 1:16 PM

Dear Francis,

Got the idea. Henrik is running one sequence on his computer at home and has travelled to the lab in Lund to start another one at the computer there. Time is tight and the computers need to run in parallel. What is the very latest time the movies need to be ready?

Best regards,
Maria

From: Francis Barany [barany@med.cornell.edu]
Sent: Sunday, May 29, 2016 3:16 PM
To: Maria Kempe; George Barany
Cc: Pearson, Matthew; Valerie Cross; Robert Hammer; Monib Zirvi; Matthew Lubin; Brian Kelly
Subject: Re: Privileged & Confidential: Memorial Weekend Summary re: Status Report regarding Cornell University, et al. v. Illumina, MOVIE 1

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(Note, in both cases the 3 blue oligo strands simultaneously are attached to the first bead, then the 3 red oligo strands simultaneously are attached to the second bead, then the 3 green oligo strands simultaneously are attached to the third bead — you already have the movie this way, do not change.)

Hope this clarifies.

All the best,

Francis

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

View less

Subject Re: Privileged & Confidential: Memorial Weekend Summary re: Status Report regarding Cornell University, et al. v. Illumina, MOVIE 1

From George Barany <barany@umn.edu>

To: Maria Kempe <maria.kempe@med.lu.se>

Cc: Francis Barany <barany@med.cornell.edu>, Pearson, Matthew <mpearson@akingump.com>, Valerie Cross <vlc1@cornell.edu>, Robert Hammer <rphammer@gmail.com>, Monib Zirvi <matzirvi@yahoo.com>, Matthew Lubin <lubingenetics@me.com>, Brian Kelly <bjk44@cornell.edu>

Date May 29, 2016 at 1:27 PM

I watched the movie and liked it a lot. Now I have a craving for popcorn. GB

On Sun, May 29, 2016 at 12:16 PM, Maria Kempe <maria.kempe@med.lu.se> wrote:

> Dear Francis,
>
> Got the idea. Henrik is running one sequence on his computer at home and has travelled to the lab in Lund to start another one at the computer there. Time is tight and the computers need to run in parallel. What is the very latest time the movies need to be ready?
>
> Best regards,
> Maria
>
> ---
>
> **From:** Francis Barany [barany@med.cornell.edu]
> **Sent:** Sunday, May 29, 2016 3:16 PM
> **To:** Maria Kempe; George Barany
> **Cc:** Pearson, Matthew; Valerie Cross; Robert Hammer; Monib Zirvi; Matthew Lubin; Brian Kelly
>
> **Subject:** Re: Privileged & Confidential: Memorial Weekend Summary re: Status Report regarding Cornell University, et al. v. Illumina, MOVIE 1

Illumina, MOVIE 1

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Hope this clarifies.

All the best,

Francis

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

View less

--
George Barany
Distinguished McKnight University Professor of
Chemistry
University of Minnesota
Department of Chemistry
[redacted]

Subject Re: Privileged & Confidential: Memorial Weekend Summary re: Status Report regarding Cornell University, et al. v. Illumina, MOVIE 1

From Francis Barany <barany@med.cornell.edu>

To: Maria Kempe <maria.kempe@med.lu.se>, Pearson, Matthew <mpearson@akingump.com>

Cc: George Barany <barany@umn.edu>, Valerie Cross <vlc1@cornell.edu>, Robert Hammer <rphammer@gmail.com>, Monib Zirvi <matzirvi@yahoo.com>, Matthew Lubin <lubingenetics@me.com>, Brian Kelly <bjk44@cornell.edu>

Date May 29, 2016 at 1:50 PM

Dear Maria & Matthew,

Understood. We need to send the reply to District Judge Stark on Thursday, June 2nd. He is different then the judge who gave us the unfavorable ruling, so this is an important chance to make a good impression.

If you need till the end of the day (Europe) on Thursday, June 2nd, then that is fine, if you email at 6:00 PM, we will get it at 12:00 PM noon.

I think your movies are terrific and would help our cause by being included in the documentation we send to District Judge Stark.

Matthew — do you concur?

Most appreciated,

Francis

[redacted]

[redacted] [redacted]
barany@med.cornell.edu

[redacted]

On May 29, 2016, at 1:16 PM, Maria Kempe <maria.kempe@med.lu.se> wrote:

Dear Francis,

Got the idea. Henrik is running one sequence on his computer at home and has travelled to the lab in Lund to start another one at the computer there. Time is tight and the computers need to run in parallel. What is the very latest time the movies need to be ready?

Best regards,
Maria

From: Francis Barany [barany@med.cornell.edu]
Sent: Sunday, May 29, 2016 3:16 PM
To: Maria Kempe; George Barany
Cc: Pearson, Matthew; Valerie Cross; Robert Hammer; Monib Zirvi; Matthew Lubin; Brian Kelly
Subject: Re: Privileged & Confidential: Memorial Weekend Summary re: Status Report regarding Cornell University, et al. v. Illumina, MOVIE 1

Dear Maria (and George),

Sorry, I fell back asleep.

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Hope this clarifies.

All the best,

Francis

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

View less

Subject Re: Privileged & Confidential: Memorial Weekend Summary re: Status Report regarding Cornell University, et al. v. Illumina, MOVIE 1

From Monib Zirvi <matzirvi@yahoo.com>

To: Francis Barany <barany@med.cornell.edu>

Cc: Maria Kempe <maria.kempe@med.lu.se>, Pearson, Matthew <mpearson@akingump.com>, George Barany <barany@umn.edu>, Valerie Cross <vlc1@cornell.edu>, Robert Hammer <rphammer@gmail.com>, Matthew Lubin <lubingenetics@me.com>, Brian Kelly <bjk44@cornell.edu>

Date May 29, 2016 at 3:23 PM

The movies are very informative and will help explain everything clearly.

Monib

Sent from my iPhone

On May 29, 2016, at 1:46 PM, Francis Barany <barany@med.cornell.edu> wrote:

Dear Maria & Matthew,

Understood. We need to send the reply to District Judge Stark on Thursday, June 2nd. He is different then the judge who gave us the unfavorable ruling, so this is an important chance to make a good impression.

If you need till the end of the day (Europe) on Thursday, June 2nd, then that is fine, if you email at 6:00 PM, we will get it at 12:00 PM noon.

I think your movies are terrific and would help our cause by being included in the documentation we

cause by being included in the documentation we send to District Judge Stark.

Matthew — do you concur?

Most appreciated,

Francis

[redacted]
barany@med.cornell.edu

[redacted]

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Best regards,
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From: Francis Barany [barany@med.cornell.edu]
Sent: Sunday, May 29, 2016 3:16 PM
To: Maria Kempe; George Barany
Cc: Pearson, Matthew; Valerie Cross; Robert Hammer; Monib Zirvi; Matthew Lubin; Brian Kelly
Subject: Re: Privileged & Confidential: Memorial Weekend Summary re: Status Report regarding Cornell University, et al. v. Illumina, MOVIE 1

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Hope this clarifies.

All the best,

Francis

[redacted]

[redacted] [redacted]

barany@med.cornell.edu

[redacted]

View less

Subject RE: Privileged & Confidential: Memorial Weekend Summary re: Status Report regarding Cornell University, et al. v. Illumina, MOVIE 1

From Maria Kempe <maria.kempe@med.lu.se>

To: Francis Barany <barany@med.cornell.edu>, Pearson, Matthew <mpearson@akingump.com>

Cc: George Barany <barany@umn.edu>, Valerie Cross <vlc1@cornell.edu>, Robert Hammer <rphammer@gmail.com>, Monib Zirvi <matzirvi@yahoo.com>, Matthew Lubin <lubingenetics@me.com>, Brian Kelly <bjk44@cornell.edu>

Date May 29, 2016 at 5:20 PM

Dear All,

Please find attached the first movie (take 2).

All the best,
Maria

From: Francis Barany [barany@med.cornell.edu]
Sent: Sunday, May 29, 2016 7:46 PM
To: Maria Kempe; Pearson, Matthew
Cc: George Barany; Valerie Cross; Robert Hammer; Monib Zirvi; Matthew Lubin; Brian Kelly
Subject: Re: Privileged & Confidential: Memorial Weekend Summary re: Status Report regarding Cornell University, et al. v. Illumina, MOVIE 1

Dear Maria & Matthew,

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I think your movies are terrific and would help our cause by being included in the documentation we send to District Judge Stark.

Matthew — do you concur?

Most appreciated,

Francis

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

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To: Maria Kempe; George Barany
Cc: Pearson, Matthew; Valerie Cross; Robert Hammer; Monib Zirvi; Matthew Lubin; Brian Kelly

Subject: Re: Privileged & Confidential: Memorial Weekend Summary re: Status Report regarding Cornell University, et al. v. Illumina, MOVIE 1

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Hope this clarifies.

All the best

All the best,

Francis

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

View less

TheFirstMovie-TakeTwo.mov

Subject Re: Privileged & Confidential: Memorial Weekend Summary re: Status Report regarding Cornell University, et al. v. Illumina, MOVIE 1

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To: Maria Kempe <maria.kempe@med.lu.se>

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Date May 29, 2016 at 5:25 PM

Dear Maria,

I realize it is 11:24 PM in Europe now…you are tireless.

This is fantastic!

Best,

Francis

[redacted]
barany@med.cornell.edu

[redacted]

> On May 29, 2016, at 5:19 PM, Maria Kempe <maria.kempe@med.lu.se> wrote:
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To: Maria Kempe; George Barany
Cc: Pearson, Matthew; Valerie Cross; Robert Hammer; Monib Zirvi; Matthew Lubin; Brian Kelly
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All the best,

Francis

[redacted]
barany@med.cornell.edu

[redacted]

<TheFirstMovie-TakeTwo.mov>

View less

Subject Re: Privileged & Confidential: Memorial Weekend Summary re: Status Report regarding Cornell University, et al. v. Illumina, MOVIE 1

From George Barany <barany@umn.edu>

To: Francis Barany <barany@med.cornell.edu>

Cc: Maria Kempe <maria.kempe@med.lu.se>, Pearson, Matthew <mpearson@akingump.com>, Valerie Cross <vlc1@cornell.edu>, Robert Hammer <rphammer@gmail.com>, Monib Zirvi <matzirvi@yahoo.com>, Matthew Lubin <lubingenetics@me.com>, Brian Kelly <bjk44@cornell.edu>

Date May 29, 2016 at 5:29 PM

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<TheFirstMovie-TakeTwo.mov>

View less

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View less

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Date May 29, 2016 at 5:39 PM

Dear Francis and George,

All credits go to my brother. He is making a great effort on this.

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| <TheFirstMovie-TakeTwo.mov>

View less

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View less

TheSecondMovie.mov

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Date May 30, 2016 at 7:17 AM

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<TheFirstMovie-TakeTwo.mov>

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View less

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Subject Re: Privileged & Confidential: Memorial Weekend Summary re: Status Report regarding Cornell University, et al. v. Illumina, MOVIE 2

From Francis Barany <barany@med.cornell.edu>

To: Maria Kempe <maria.kempe@med.lu.se>

Cc: George Barany <barany@umn.edu>, Pearson, Matthew <mpearson@akingump.com>, Valerie Cross <vlc1@cornell.edu>, Robert Hammer <rphammer@gmail.com>, Monib Zirvi <matzirvi@yahoo.com>, Matthew Lubin <lubingenetics@me.com>, Brian Kelly <bjk44@cornell.edu>

Date May 30, 2016 at 8:26 AM

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<TheSecondMovie.mov>

View less

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Date May 30, 2016 at 8:54 AM

Dear GB & Maria,

Maybe Toy Story I, II, and III?

(It will actually be 5 movies, for parts A, B, C, and already completed D & E).

Please no comparison to the “Rocky” series!

Later,

FB

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(iii) We attach the oligos to the beads, one sequence (color) at a time.

Movie 2 (Version E).

(i) We etch the three wells into the glass slide.

(ii) We attach the oligos to the beads, one sequence (color) at a time.

(iii) We drop all the beads into the wells at the same time.

(Note, in both cases the 3 blue oligo strands simultaneously are attached to the first bead, then the 3 red oligo strands simultaneously are attached to the second bead, then the 3 green oligo strands simultaneously are attached to the third bead — you already have the movie this

way, do not change.)

Hope this clarifies.

All the best,

Francis

[redacted]
barany@med.cornell.edu

[redacted]

<TheFirstMovie-TakeTwo.mov>

--
George Barany
Distinguished McKnight University Professor of Chemistry
University of Minnesota
Department of Chemistry
[redacted]

--
George Barany
Distinguished McKnight University Professor of Chemistry
University of Minnesota
Department of Chemistry
[redacted]

<TheSecondMovie.mov>

--
George Barany

Distinguished McKnight University Professor of Chemistry
University of Minnesota
Department of Chemistry
[redacted]

View less

Subject Re: Privileged & Confidential: Memorial Weekend Summary re: Status Report regarding Cornell University, et al. v. Illumina, MOVIE 2

From George Barany <barany@umn.edu>

To: Francis Barany <barany@med.cornell.edu>

Cc: Maria Kempe <maria.kempe@med.lu.se>, Pearson, Matthew <mpearson@akingump.com>, Valerie Cross <vlc1@cornell.edu>, Robert Hammer <rphammer@gmail.com>, Monib Zirvi <matzirvi@yahoo.com>, Matthew Lubin <lubingenetics@me.com>, Brian Kelly <bjk44@cornell.edu>

Date May 30, 2016 at 9:01 AM

nor Star Wars comparisons ... they couldn't even make those movies in chronological order

On Mon, May 30, 2016 at 7:53 AM, Francis Barany <barany@med.cornell.edu> wrote:

> Dear GB & Maria,
>
> Maybe Toy Story I, II, and III?
>
> (It will actually be 5 movies, for parts A, B, C, and already completed D & E).
>
> Please no comparison to the “Rocky” series!
>
> Later,
>
> FB
>
> > On May 30, 2016, at 8:49 AM, George Barany <barany@umn.edu> wrote:

If it's a trilogy, let the record show that I am withdrawing my Godfather analogy! GB

On Mon, May 30, 2016 at 7:32 AM, Maria Kempe <maria.kempe@med.lu.se> wrote:

Dear Francis and George,

Glad you like it! Henrik is working on the third part of the trilogy right now.

Have a nice Memorial Day.

All the best,
Maria

From: Francis Barany [barany@med.cornell.edu]
Sent: Monday, May 30, 2016 2:22 PM
To: Maria Kempe
Cc: George Barany; Pearson, Matthew; Valerie Cross; Robert Hammer; Monib Zirvi; Matthew Lubin; Brian Kelly
Subject: Re: Privileged & Confidential: Memorial Weekend Summary re: Status Report regarding Cornell University, et al. v. Illumina, MOVIE 2

Dear Maria,

I love the way the beads roll in on the right…

(I agree with George, the second movie is even better than the first).

Thank you and thank Henrik for such a marvelous job on this.

I will discuss with Matthew and Valerie tomorrow (it's a holiday today in the US).

All the best,

Francis

[redacted]
barany@med.cornell.edu

[redacted]

On May 30, 2016, at 7:17 AM, George Barany <barany@umn.edu> wrote:

ike The Godfather, Part II is even better than the already fabulous Part I.

> On May 30, 2016, at 6:00 AM, Maria Kempe <maria.kempe@med.lu.se> wrote:
>
> Dear All,
>
> Please find attached the second movie.
>
> Best regards,
> Maria
>
> ---
>
> **From:** Francis Barany [barany@med.cornell.edu]
> **Sent:** Sunday, May 29, 2016 11:34 PM
> **To:** George Barany
> **Cc:** Maria Kempe; Pearson, Matthew; Valerie Cross; Robert Hammer; Monib Zirvi; Matthew Lubin; Brian Kelly
> **Subject:** Re: Privileged & Confidential: Memorial Weekend Summary re: Status Report regarding Cornell University, et al. v. Illumina, MOVIE 1
>
> That will all be taken care of…
>
> Later, FB
>
> > On May 29, 2016, at 5:30 PM, George Barany <barany@umn.edu> wrote:
> >
> > will the movie get a more formal name -- "The First Movie-TakeTwo" may be ok for "internal" use but should be changed before it is presented to a judge
> >
> > On Sun, May 29, 2016 at 4:29 PM, George Barany <barany@umn.edu> wrote:

Barany <barany@uhm.edu> wrote:

<image.png>

On Sun, May 29, 2016 at 4:25 PM, Francis Barany <barany@med.cornell.edu> wrote:

Dear Maria,

I realize it is 11:24 PM in Europe now…you are tireless.

This is fantastic!

Best,

Francis

[redacted]

barany@med.cornell.edu

[redacted]

On May 29, 2016, at 5:19 PM, Maria Kempe <maria.kempe@med.lu.se> wrote:

Dear All,

Please find attached the first movie (take 2).

All the best,
Maria

From: Francis Barany [barany@med.cornell.edu]
Sent: Sunday, May 29, 2016 7:46 PM
To: Maria Kempe; Pearson, Matthew

Cc: George Barany; Valerie Cross; Robert Hammer; Monib Zirvi; Matthew Lubin; Brian Kelly
Subject: Re: Privileged & Confidential: Memorial Weekend Summary re: Status Report regarding Cornell University, et al. v. Illumina, MOVIE 1

Dear Maria & Matthew,

Understood. We need to send the reply to District Judge Stark on Thursday, June 2nd.

He is different then the judge who gave us the unfavorable ruling, so this is an important chance to make a good impression.

If you need till the end of the day (Europe) on Thursday, June 2nd, then that is fine, if you email at 6:00 PM, we will get it at 12:00 PM noon.

I think your movies are terrific and would help our cause by being included in the documentation we send to District Judge Stark.

Matthew — do you concur?

Most appreciated,

Francis

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

On May 29, 2016, at 1:16 PM, Maria Kempe <maria.kempe@med.lu.se> wrote:

Dear Francis,

Got the idea. Henrik is running one sequence on his computer at home and has travelled to the lab in Lund to start another one at the computer there. Time is tight and the computers need to run in parallel. What is the very latest time the movies need to be ready?

Best regards,
Maria

From: Francis Barany [barany@med.cornell.edu]
Sent: Sunday, May 29, 2016 3:16 PM
To: Maria Kempe; George Barany
Cc: Pearson, Matthew; Valerie Cross; Robert Hammer; Monib Zirvi; Matthew Lubin; Brian Kelly

Subject: Re: Privileged & Confidential: Memorial Weekend Summary re: Status Report regarding Cornell University, et al. v. Illumina, MOVIE 1

Dear Maria (and George),

Sorry, I fell back asleep.

1. GB, movie is attached again below. You can just click on it to run it. If you want to drag to you desktop, right click on the image, choose “view as icon”, hen drag the icon wherever you want. You need “Quicktime" on your computer.

2. Maria, please follow the following directions for the two movies, so they are as similar as possible.

Opening scene: We see the glass slide. We see the three cream-colored beads in a row, with some space between them (can be the same or different from the spacing when they are dropped onto the glass).

Movie 1 (Version D).

(i) We etch the three wells into the glass slide.

(ii) We drop all the beads into the wells at the same time.

(iii) We attach the oligos to the beads, one sequence (color) at a time.

Movie 2 (Version E).

(i) We etch the three wells into the glass slide.

(ii) We attach the oligos to the beads, one sequence (color) at a time.

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Hope this clarifies.

All the best,

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[redacted]
barany@med.cornell.edu

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University of Minnesota
Department of Chemistry
[redacted]

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University of Minnesota
Department of Chemistry
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<TheSecondMovie.mov>

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Chemistry
University of Minnesota
Department of Chemistry
[redacted]

View less

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George Barany
Distinguished McKnight University Professor of
Chemistry
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Subject Re: Privileged & Confidential: Memorial Weekend Summary re: Status Report regarding Cornell University, et al. v. Illumina, MOVIE 1

From Francis Barany <barany@med.cornell.edu>

To: Maria Kempe <Maria.Kempe@med.lu.se>, George Barany <barany@umn.edu>, Robert Hammer <rphammer@gmail.com>

Cc: Pearson, Matthew <mpearson@akingump.com>, Valerie Cross <vlc1@cornell.edu>, Monib Zirvi <matzirvi@yahoo.com>, Matthew Lubin <lubingenetics@me.com>, Brian Kelly <bjk44@cornell.edu>, Francis Barany <barany@med.cornell.edu>

Date May 30, 2016 at 6:58 PM

Dear Maria, Bob, and GB,

One additional thought occurred to me….

Bob pointed out that Illumina's argument now entirely hinges on the 120 amended claim (reproduced below so you don't need to look for it), where we removed the word "support" from the last clause.

However, the word "support" is actually redundant, because the previous clause already used the word as "a solid support".

As Maria has written so elegantly in her comments, the solid support is the result of combining the substrate with the surface. Thus, the linker may be used to couple the oligo to the solid support- which comprises all he examples of composites made of the substrate and the surface.

Here is my first question: How many substrates do we mention? Do we call the bead a substrate, a support, or a surface? Can the bead be a support in

support, or a surface? Can the bead be a support in one definition, and a surface in another? The bead has a surface, and that surface interacts with the solid support (i.e. Etched glass), and also is suitable for attaching an oligonucleotide. Do we mention substrates other than glass?

Next, how many surfaces do we mention? The surface can be a composite, i.e. It can be a polystyrene bead with a pegylated surface. It can be a silica bead with a silane coating, and then a silane surface. Or, it can be a glass slide with a silane coating and a polymer surface.

Again, how many different surfaces do we describe in the patent?

Finally, if we multiply the number of substrates by the number of surfaces, how many different configurations of solid supports do we cover in the patent? In the "Markman_response_Figures_v04_MK_FB.pptx" powerpoint (also enclosed as pdf) we illustrate 12 examples of combining substrates with surfaces to generate solid supports. However, I believe there are more potential combinations covered in the actual patent.

We need to win this one unambiguously...

Thanks a million!

Francis

[redacted]
barany@med.cornell.edu

[redacted]

In the '917 specs, we have the following paragraphs:

The solid support can be made from a wide variety of materials. The substrate may be biological, nonbiological, organic, inorganic, or a combination of any of these,

existing as particles, strands, precipitates, gels, sheets, tubing, spheres, containers, capillaries, pads, slices, films, plates, slides, discs, membranes, etc. The substrate may have any convenient shape, such as a disc, square, circle, etc. The substrate is preferably flat but may take on a variety of alternative surface configurations. For example, the substrate may contain raised or depressed regions on which the synthesis takes place. The substrate and its surface preferably form a rigid support on which to carry out the reactions described herein. The substrate and its surface is also chosen to provide appropriate light-absorbing characteristics. For instance, the substrate may be a polymerized Langmuir Blodgett film, functionalized glass, Si, Ge, GaAs, GaP, SiO.sub.2, SiN.sub.4, modified silicon, or any one of a wide variety of gels or polymers such as (poly)tetrafluoroethylene, (poly)vinylidenedifluoride, polystyrene, polycarbonate, polyethylene, polypropylene, polyvinyl chloride, poly(methyl acrylate), poly(methyl methacrylate), or combinations thereof. Other substrate materials will be readily apparent to those of ordinary skill in the art upon review of this disclosure. In a preferred embodiment, the substrate is flat glass or single-crystal silicon.

According to some embodiments, the surface of the substrate is etched using well known techniques to provide for desired surface features. For example, by way of the formation of trenches, v-grooves, mesa structures, raised platforms, or the like, the synthesis regions may be more closely placed within the focus point of impinging light, be provided with reflective "mirror" structures for maximization of light collection from fluorescent sources, or the like.

Surfaces on the solid substrate will usually, though not always, be composed of the same material as the substrate. Thus, the surface may be composed of any of a

wide variety of materials, for example, polymers, plastics, ceramics, polysaccharides, silica or silica-based materials, carbon, metals, inorganic glasses, membranes, or composites thereof. The surface is functionalized with binding members which are attached firmly to the surface of the substrate. Preferably, the surface functionalities will be reactive groups such as silanol, olefin, amino,

hydroxyl, aldehyde, keto, halo, acyl halide, or carboxyl groups. In some cases, such functionalities preexist on the substrate. For example, silica based materials have silanol groups, polysaccharides have hydroxyl groups, and synthetic polymers can contain a broad range of functional groups, depending on which monomers they are produced from. Alternatively, if the substrate does not contain the desired functional groups, such groups can be coupled onto the substrate in one or more steps.

Example 1

Immobilization of capture oligonucleotides to solid supports

The solid support for immobilization was glass, in particular microscope slides The immobilization to glass (e.g., microscope slides), or other supports such as silicon (e.g., chips), membranes (e.g., nylon membranes), beads (e.g., paramagnetic or agarose beads), or plastics supports (e.g., polyethylene sheets) of capture oligonucleotides in spatially addressable arrays is comprised of 5 steps:

What is claimed:

1. A device comprising: a solid support having an array of positions each suitable for attachment of an oligonucleotide probe; a linker suitable for coupling an oligonucleotide probe to the solid support and attached to the solid support at each of the array positions; and an array of capture oligonucleotide probes on the solid support at the array positions, said capture oligonucleotide probes each having greater than sixteen nucleotides and able to bind to complementary nucleic acids at uniform hybridization conditions, wherein each capture oligonucleotide probe of the array differs in sequence from its adjacent capture oligonucleotide probe, when aligned to each other by at least 25% of the nucleotides.

2. The device according to claim 1, wherein different capture oligonucleotide probes are attached at different array positions on the solid support to detect different nucleic acids.

3. The device according to claim 1, wherein the solid

support is made from a material selected from the group consisting of plastic, ceramic, metal, resin, gel, glass, silicon, and composites thereof.

4. The device according to claim 1, wherein the solid support is in a form selected from the group consisting of slides, discs, membranes, films, and composites thereof.

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Markman_response_Figures_v04_MK_…

ATT00002.htm

ATT00003.htm

Subject Re: Privileged & Confidential: Memorial Weekend Summary re: Status Report regarding Cornell University, et al. v. Illumina, MOVIE 1

From Maria Kempe <maria.kempe@med.lu.se>

To: Francis Barany <barany@med.cornell.edu>

Cc: George Barany <barany@umn.edu>, Robert Hammer <rphammer@gmail.com>, Pearson, Matthew <mpearson@akingump.com>, Valerie Cross <vlc1@cornell.edu>, Monib Zirvi <matzirvi@yahoo.com>, Matthew Lubin <lubingenetics@me.com>, Brian Kelly <bjk44@cornell.edu>

Date May 30, 2016 at 8:07 PM

Dear All,

Just a short reply in the middle of my night from my ipad: I made an alternative master figure A-E the other day where I named the beads in D and E "substrate" and the silanized beads "solid support" .... The result is solid support + solid support --> solid support

The alternative figure is on my laptop but I can not send it now because the laptop is in the lab rendering movies (we use 3 computers now to speed it up). I will send it tomorrow.

All the best,
Maria

Skickat från min iPad

> 31 maj 2016 kl. 00:58 skrev Francis Barany

<barany@med.cornell.edu>:
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Date May 30, 2016 at 8:18 PM

I will be available tomorrow for most of 7 a.m. - noon, CDT, if anyone wants to talk to me on the phone or on skype. I will only make one very general comment now, that you can all interpret as you will -- at the time that we described our invention, I had recently written several original research papers and review articles which covered the full range of solid-phase supported methodologies in two and three dimensions, with the full range of materials that had been explored up to that time. These writings were used in the crafting of the various sections of the patent applications. To me, there are no surprises here. GB

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George Barany
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Date May 30, 2016 at 9:21 PM

Dear Maria and George,

Maria, after careful consideration, I am afraid the approach of solid support + solid support --> Solid support will be counter-productive.

Since we did not pursue claim 120 of "solid support plus (linker) or support", we will not win any argument based on solid support + solid support —> Solid support.

I believe a more productive approach is to stick with the definitions within the patent application: Substrate + Surface —> Solid Support.

I have no problem with the “surface” being a bead that is silanized, fits in a well, and has oligo covalently attached to it. The many beads fitting into an etched glass substrate represents the full "solid support having an array of positions, each suitable for attachment of an oligonucleotide probe."

So once again, from the patent, kindly focus on:

Substrate + Surface
—> Solid Support.

Please list all the substrates, all the potential surfaces, and then all the different solid supports that could arise.

If every combination works, , then for example, we describe 3 different substrates, 5 different silanized surfaces that work either directly or with 2 different polymers, this would give us:

3 Substrates
X 5 Surfaces X (1 no polymer + 2 polymers)
= 3 x 5 x 3 = 45 Solid Supports.

If not every combination works, then for example, we describe 3 different substrates, 4 different silanized surfaces which may be used directly, or 3 of those surfaces may be linked to 2 different polymers, this would give us:

3 Substrates
X 4 Surfaces X no polymer
= 12 Solid Supports.

3 Substrates
X 3 Surfaces X 2 polymers
= 18 Solid Supports.

For this example, a total of 30 different solid supports.

Please try to do the calculation as best you can — does not have to be fully accurate, but if we can show that the patent covered over 30 examples of composite solid supports, or better yet, over 100 examples, that becomes a powerful argument as to why we didn't press the alternate claim 120 of "solid support plus support", because we already had it covered in earlier claims…

George: since you say there are no surprises, would you kindly email to all your list of (substrates) and (surfaces)?

Right now, the figures are perfect, the extra movies are coming — what's important is to provide the total number of different solid supports described such that Judge Stark goes:

"Yeah, got it, the specifications and claims already covered over 100 different variations of Substrate + Surface —> Solid Support, all different types of composites, glass to polymer that feels like jello, glass to beads, now I understand why they didn't waste the examiner's time asking for "solid support plus support" — we will go with the definition of solid support including composite materials and strike the use of "a single unitary substrate" as they already have so many examples to the contrary.

Please provide these numbers by 6 PM Swedish time = 12:00 noon New York time. They don't have to be capturing every variation (etched surfaces vs. ridges), but they should cover most of the chemistry. I would like to be able to have Matthew include a comment along the lines of "Over 100 different composite solid supports, comprising of different substrates and surfaces were described…"

Maria — would you kindly provide me with your phone number(s) where I can reach you tomorrow if needed? Please include country code. Alternatively, I can do a webex in my morning = your afternoon...

Hope this helps

Francis

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

———————————————

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Date May 30, 2016 at 9:39 PM

I am home tonight and all my hard copy printouts and all my books are in my office. I did read very carefully the e-mail you sent to everyone more than a week ago (before my weekend trip to Chicago--you had pasted in large sections of the patent. As I remember, all the variations were claimed, and we had specific examples of some of them. When Matthew and Angela visited me a few times almost a year ago, I think that I loaned some of my reviews from that time, including the one on which Gregg Fields was first author (book edited by Gregory Grant) and the one on which Maria was first author (book edited by Anthony Czarnik and Sheila DeWitt). GB

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Francis

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>
> Just a short reply in the middle of my night from my ipad: I made an alternative master figure A-E the other day where I named the beads in D and E "substrate" and the silanized beads "solid support" .... The result is solid support + solid

support --> solid support

The alternative figure is on my laptop but I can not send it now because the laptop is in the lab rendering movies (we use 3 computers now to speed it up). I will send it tomorrow.

All the best,
Maria

Skickat från min iPad

> 31 maj 2016 kl. 00:58 skrev Francis Barany <barany@med.cornell.edu>:
>
> Do we call the bead a substrate, a support, or a surface? Can the bead be a support in one definition, and a surface in another? T

View less

--
George Barany
Distinguished McKnight University Professor of Chemistry
University of Minnesota
Department of Chemistry
[redacted]

Subject Privileged & Confidential: Memorial Weekend Summary re: Status Report regarding Cornell University, et al. v. Illumina, MOVIE 1 and more

From Matthew Lubin <lubingenetics@me.com>

To: Barany Francis <barany@med.cornell.edu>, Maria Kempe <maria.kempe@med.lu.se>, Robert Hammer <rphammer@gmail.com>, Pearson, Matthew <mpearson@akingump.com>, Valerie Cross <vlc1@cornell.edu>, Monib Zirvi <matzirvi@yahoo.com>, <barany@umn.edu>

Date May 31, 2016 at 1:05 AM

To all,

Although I haven't chimed in until now, I just want to let everyone know that I have followed the correspondence of the last couple of weeks with interest. As a simple clinician now, I can still follow the discussion but I am afraid that I have little to contribute, especially on the on the topics of supports, surfaces and arrays. The quality of the movies and the explanations behind them are wonderful and will hopefully accomplish their intended purpose. I thank everybody for the diligence put forth on behalf of all and look forward to our success.

Thanks again.

Matthew Lubin

Subject Re: Privileged & Confidential: Cookies and Pie Analogy re: Status Report regarding Cornell University, et al. v. Illumina

From Francis Barany <barany@med.cornell.edu>

To: Maria Kempe <maria.kempe@med.lu.se>, George Barany <barany@umn.edu>, Robert Hammer <rphammer@gmail.com>

Cc: Pearson, Matthew <mpearson@akingump.com>, Valerie Cross <vlc1@cornell.edu>, Monib Zirvi <matzirvi@yahoo.com>, Matthew Lubin <lubingenetics@me.com>, Brian Kelly <bjk44@cornell.edu>

Date May 31, 2016 at 7:41 AM

Dear Maria, George, and Bob,

Not sure I'm communicating properly here, let's try a slightly different approach.

From the specifications below, there are 18 substrates or combinations thereof.

There are 10 surfaces or composites thereof, including 9 surface functionalities.

At a minimum, the 18 substrates may be combined with the 10 surfaces, some of which will already have a functionality, others may have multiple possible functionalities, say total is no less than 20 — are we talking about no less than 360 different potential solid supports?

If the numbers above are incorrect, then PLEASE provide the correct total number of ways (or a minimum number based on the specifications) of making solid supports.

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Would you PLEASE fill in the substrate + surface = solid support (in chemistry terms). You can use any of the 12 examples 5A-5L to guide you, and if I have the wrong food analogy, please change to fit the chemistry.

Cookie with embedded peanuts M & M =
(Cookie Dough = etched glass substrate; Peanuts = beads; Colored candy/chocolate surface of M & M = functionalized surface of beads).

Chocolate cream pie =
(Pie crust = glass substrate; Chocolate = silanized surface or first polymer layer; Cream = second polymer layer; Chocolate toppings = oligos)

(See enclosed photos)

I think it should be clear to you that the first analogy is the one we want to implant in the judges mind, but having additional ones just reiterates that we have covered MANY different ways of combining substrates with surfaces to form solid supports.

Thanks a million!

Francis

[redacted]

barany@med.cornell.edu

The solid support can be made from a wide variety of materials. The substrate may be biological, nonbiological, organic, inorganic, or a combination of any of these, existing as particles, strands, precipitates, gels, sheets, tubing, spheres, containers, capillaries, pads, slices, films, plates, slides, discs, membranes, etc. The substrate may have any convenient shape, such as a disc, square, circle, etc. The substrate is preferably flat but may take on a variety of alternative surface configurations. For example, the substrate may contain raised or depressed regions on which the synthesis takes place. The substrate and its surface preferably form a rigid support on which to carry out the reactions described herein. The substrate and its surface is also chosen to provide appropriate light-absorbing characteristics. For instance, the substrate may be a polymerized Langmuir Blodgett film, functionalized glass, Si, Ge, GaAs, GaP, SiO.sub.2, SiN.sub.4, modified silicon, or any one of a wide variety of gels or polymers such as (poly)tetrafluoroethylene, (poly)vinylidenedifluoride, polystyrene, polycarbonate, polyethylene, polypropylene, polyvinyl chloride, poly(methyl acrylate), poly(methyl methacrylate), or combinations thereof. Other substrate materials will be readily apparent to those of ordinary skill in the art upon review of this disclosure. In a preferred embodiment, the substrate is flat glass or single-crystal silicon.

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Sent: Tuesday, May 31, 2016 1:40 PM
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View less

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Sent from my iPhone

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Date May 31, 2016 at 9:20 AM

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I am sending an array princess cake. Please also find a paper - it is cited in the patent (26: 7) - I am not sure if it is already in the previous collection. It shows glass + gold + dextran.

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Sent: Tuesday, May 31, 2016 3:04 PM
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barany@med.cornell.edu

[redacted]

The solid support can be made from a wide variety of materials. The substrate may be biological, nonbiological, organic, inorganic, or a combination of any of these, existing as particles, strands, precipitates, gels, sheets, tubing, spheres, containers, capillaries, pads, slices, films, plates, slides, discs, membranes, etc. The substrate may have any convenient shape, such as a disc, square, circle, etc. The substrate is preferably flat but may take on a variety of alternative surface configurations. For example, the substrate may contain raised or depressed regions on which the synthesis takes place. The substrate and its surface preferably form a rigid support on which to carry out the reactions described herein. The substrate and its surface is also chosen to provide appropriate light-absorbing

characteristics. For instance, the substrate may be a polymerized Langmuir Blodgett film, functionalized glass, Si, Ge, GaAs, GaP, SiO.sub.2, SiN.sub.4, modified silicon, or any one of a wide variety of gels or polymers such as (poly)tetrafluoroethylene, (poly)vinylidenedifluoride, polystyrene, polycarbonate, polyethylene, polypropylene, polyvinyl chloride, poly(methyl acrylate), poly(methyl methacrylate), or combinations thereof. Other substrate materials will be readily apparent to those of ordinary

skill in the art upon review of this disclosure. In a preferred embodiment, the substrate is flat glass or single-crystal silicon.

18 substrates or combinations thereof

Surfaces on the solid substrate will usually, though not always, be composed of the same material as the substrate. Thus, the surface may be composed of any of a wide variety of materials, for example, polymers, plastics, ceramics, polysaccharides, silica or silica-based materials, carbon, metals, inorganic glasses, membranes, or composites thereof. The surface is functionalized with binding members which are attached firmly to the surface of the substrate. Preferably, the surface functionalities will be reactive groups such as silanol, olefin, amino, hydroxyl, aldehyde, keto, halo, acyl halide, or carboxyl groups. In some cases, such functionalities preexist on the substrate. For example, silica based materials have silanol groups, polysaccharides have hydroxyl groups, and synthetic polymers can contain a broad range of functional groups, depending on which monomers they are produced from. Alternatively, if the substrate does not contain the desired functional groups, such groups can be coupled onto the substrate in one or more steps.

10 surfaces or composites thereof

9 surface functionalities.

A variety of commercially-available materials, which

include suitably modified glass, plastic, or carbohydrate surfaces or a variety of membranes, can be used. Depending on the material, surface functional groups (e.g., silanol, hydroxyl, carboxyl, amino) may be present from the outset (perhaps as part of the coating polymer), or will require a separate procedure (e.g., plasma amination, chromic acid oxidation, treatment with a functionalized side chain alkyltrichlorosilane) for introduction of the functional group. Hydroxyl groups become incorporated into stable carbamate (urethane) linkages by several methods. Amino functions can be acylated directly, whereas carboxyl groups are activated, e.g., with N,N'-carbonyldiimidazole or water-soluble

carbodiimides, and reacted with an amino-functionalized compound. As shown in FIG. 11, the solid supports can be membranes or surfaces with a starting functional group X. Functional group transformations can be carried out in a variety of ways (as needed) to provide group X* which represents one partner in the covalent linkage with group Y*. FIG. 11 shows specifically the grafting of PEG (i.e. polyethylene glycol), but the same repertoire of reactions can be used (however needed) to attach carbohydrates (with hydroxyl), linkers (with carboxyl), and/or oligonucleotides that have been extended by suitable functional groups (amino or carboxyl). In some cases, group X* or Y* is pre-activated (isolatable species from a separate reaction); alternatively, activation occurs in situ. Referring to PEG as drawn in FIG. 11, Y and Y* can be the same (homobifunctional) or different (heterobifunctional); in the latter case, Y can be protected for further control of the chemistry. Unreacted amino groups will be blocked by acetylation or succinylation, to ensure a neutral or negatively charged environment that "repels" excess unhybridized DNA. Loading levels can be determined by standard analytical methods. Fields, et al., "Principles and Practice of Solid-Phase Peptide Synthesis," Synthetic Peptides: A User's Guide. G. Grant, Editor, W.H. Freeman and Co.: New York. p. 77 183 (1992), which is hereby incorporated by reference.

Not sure how to calculate these surface functionalities.

At a minimum, the 18 substrates may be combined with the 10 surfaces, some of which will already have a functionality, others may have multiple possible functionalities, say total is no less than 20 — are we talking about no less than 360 different potential solid supports?

<Cookies with peanut M&Ms.jpg>

<chocolate_cream_pie.jpg>

<Movie A (BareSilicaSurface).mov>
<Movie B (Polymer).mov>
<Movie C (NoodlesTheMovie).mov>

View less

Lofas 1990 (glass+gold+dextran).pdf

Subject Re: Privileged & Confidential: Cookies and Pie Analogy re: Status Report regarding Cornell University, et al. v. Illumina

From Robert Hammer <rphammer@gmail.com>

To: Francis Barany <barany@med.cornell.edu>

Cc: Maria Kempe <maria.kempe@med.lu.se>, George Barany <barany@umn.edu>, Pearson, Matthew <mpearson@akingump.com>, Valerie Cross <vlc1@cornell.edu>, Monib Zirvi <matzirvi@yahoo.com>, Matthew Lubin <lubingenetics@me.com>, Brian Kelly <bjk44@cornell.edu>

Date May 31, 2016 at 9:30 AM

Francis:

Here is my stab at the language for the solid-support = substrate + surface:

As described in the patent, the solid-support can be made up of 18 different substrates in combination with 10 different surfaces containing appropriate functionality for chemistry required. For example the substrate could be a metal, such as aluminum, with a layer of polysaccharide (dextran) as the surface. This dextran surface is adhered to the substrate by non-covalent forces. The surface of dextran has hydroxyl groups that could used for attachment of the oligonucleotides by any variety of chemistries as described in the patent, including N,N'-carbonyldiimidazole. Another example could be an etched glass substrate in which a polymer coating of polyethylene acts as the surface. Again this polymer is adhered to the surface by non-covalent

forces such as hydrophobic interactions. To create a better adherance, the substrate glass could be silanized with a hydrophobic group such

silanized with a hydrophobic group such dimethydichlorosilane. To provide functionality to the polyethylene surface one can oxidize the surface to produce carboxylate functionality which are readily activated to provide covalent attachment of oligonucleotides. For example the carboxylates are activated by a carbodiimide and an amine-functionalized is added to form an amide bond attachment. Another example could be a glass substrate. The surface could be provided by silica or polystyrene beads that are adhered to the surface non-covalently or covalently. For covalent attachment of the beads, one creates a composite bead by attaching a functionalized polymer coating such a polyethylene glycol to the bead. The resulting solid-support is a combination of a glass surface with a composite bead attached to the glass. These techniques were well known to those skilled in the art at the time the patent was filed. As provided in the description, we provided 18 different surfaces with 10 different substrates to clearly provide at least 180 different composite solid-supports. More are possible as combinations of substrates and surface was described in the patent. So a substrate could be a glass substrate with a gold layer with a dextran layer added as the surface to make up the solid-support (REF from MARIA). The patent thus describes a wide range of combinations of materials that provide multilayered composite solid-supports, that in no way could be considered "single unitary substrates".

I have to go to some meetings this AM.

I will do more at lunch.

Bob

On Tue, May 31, 2016 at 7:40 AM, Francis Barany <barany@med.cornell.edu> wrote:

> Dear Maria, George, and Bob,

Not sure I'm communicating properly here, let's try a slightly different approach.

From the specifications below, there are 18 substrates or combinations thereof.

There are 10 surfaces or composites thereof, including 9 surface functionalities.

At a minimum, the 18 substrates may be combined with the 10 surfaces, some of which will already have a functionality, others may have multiple possible functionalities, say total is no less than 20 — are we talking about no less than 360 different potential solid supports?

If the numbers above are incorrect, then PLEASE provide the correct total number of ways (or a minimum number based on the specifications) of making solid supports.

When using spheres or beads, one can think of this in two ways: (i) The substrate is a combination of etched glass plate and multiple silica or polystyrene beads, the later being functionalized with the appropriate chemistry — when these are combined they create the solid support. (ii) The substrate is the etched glass plate, and the surface is multiple beads of silica-based material, polymers, or glasses, that are functionalized with the appropriate chemistry.

It is clear to me the judge (interns) do not understand the chemistry here. They have reduced it to incorrect analogies like varnish on a table or plywood. However, I think Maria had an excellent idea when she started in with the cake

analogy. This is important as we can help the judge understand when you are making a cake then the layers are composites.

<u>Would you PLEASE fill in the substrate + surface = solid support (in chemistry terms)</u>. You can use any of the 12 examples 5A-5L to guide you, and if I have the wrong food analogy, please change to fit

have the wrong food analogy, please change to fit the chemistry.

Cookie with embedded peanuts M & M =
(Cookie Dough = etched glass substrate; Peanuts = beads; Colored candy/chocolate surface of M & M = functionalized surface of beads).

Chocolate cream pie =
(Pie crust = glass substrate; Chocolate = silanized surface or first polymer layer; Cream = second polymer layer; Chocolate toppings = oligos)

(See enclosed photos)

I think it should be clear to you that the first analogy is the one we want to implant in the judges mind, but having additional ones just reiterates that we have covered MANY different ways of combining substrates with surfaces to form solid supports.

Thanks a million!

Francis

[redacted]
barany@med.cornell.edu

[redacted]

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View less

Subject Re: Privileged & Confidential: Cookies and Pie Analogy re: Status Report regarding Cornell University, et al. v. Illumina

From Francis Barany <barany@med.cornell.edu>

To: Robert Hammer <rphammer@gmail.com>, Maria Kempe <maria.kempe@med.lu.se>, George Barany <barany@umn.edu>

Cc: Pearson, Matthew <mpearson@akingump.com>, Valerie Cross <vlc1@cornell.edu>, Monib Zirvi <matzirvi@yahoo.com>, Matthew Lubin <lubingenetics@me.com>, Brian Kelly <bjk44@cornell.edu>

Date May 31, 2016 at 10:24 AM

Dear Bob, Maria, and George,

I spoke with all of you this morning.

Maria, your movies are excellent — we discussed how to put your beautiful movies and chemistry into context that a jury will understand — FOOD!

Kindly see attached some additional pictures I downloaded from google images that cover (i) peanut butter on toast, (ii) peanut butter and jelly on toast, (iii) peanut butter and banana on toast, (iv) peanut butter and blueberries on toast, (v) peanut butter and mixed berries on toast, and (iv) peanut butter and avocado on toast.

These should be able to cover your Movies A, B, C, D & E. — (just use (v) peanut butter and mixed berries on toast as the SAME example for D & E.) You now need to just provide the chemistry that matches with the food picture and the movie.

Also, kindly provide us some numbers of the total number of solid supports covered in the patent, i.e. multiply substrate times (simple + composite)

multiply substrate times (simple + composite) surface…

Bob, your description below is very helpful in plain language…

Best,

Francis

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

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I have to go to some meetings this AM.

I will do more at lunch.

Bob

Subject RE: Privileged & Confidential: Cookies and Pie Analogy re: Status Report regarding Cornell University, et al. v. Illumina

From Maria Kempe <maria.kempe@med.lu.se>

To: Francis Barany <barany@med.cornell.edu>, Robert Hammer <rphammer@gmail.com>, George Barany <barany@umn.edu>

Cc: Pearson, Matthew <mpearson@akingump.com>, Valerie Cross <vlc1@cornell.edu>, Monib Zirvi <matzirvi@yahoo.com>, Matthew Lubin <lubingenetics@me.com>, Brian Kelly <bjk44@cornell.edu>

Date May 31, 2016 at 6:00 PM

Dear Francis and All,

The food analogs were a little tricky. Please find attached an attempt along these lines. Will the food analogs be used with the judge or are the idea only to use them with the jury next year? If the latter, my suggestion is that we work some more on this during the coming year.

All the best,
Maria

From: Francis Barany [barany@med.cornell.edu]
Sent: Tuesday, May 31, 2016 4:23 PM
To: Robert Hammer; Maria Kempe; George Barany
Cc: Pearson, Matthew; Valerie Cross; Monib Zirvi; Matthew Lubin; Brian Kelly
Subject: Re: Privileged & Confidential: Cookies and Pie Analogy re: Status Report regarding Cornell University, et al. v. Illumina

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Bob

View less

MK Food equivalencies 160531 .docx

Subject Re: Privileged & Confidential: Cookies and Pie Analogy re: Status Report regarding Cornell University, et al. v. Illumina

From George Barany <barany@umn.edu>

To: Maria Kempe <maria.kempe@med.lu.se>

Cc: Francis Barany <barany@med.cornell.edu>, Robert Hammer <rphammer@gmail.com>, Pearson, Matthew <mpearson@akingump.com>, Valerie Cross <vlc1@cornell.edu>, Monib Zirvi <matzirvi@yahoo.com>, Matthew Lubin <lubingenetics@me.com>, Brian Kelly <bjk44@cornell.edu>

Date May 31, 2016 at 6:16 PM

Looks delicious! Don't forget cream-puffs with chocolate sprinkles on the outside. 😁 GB

On Tue, May 31, 2016 at 5:00 PM, Maria Kempe <maria.kempe@med.lu.se> wrote:

> Dear Francis and All,
>
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> Maria
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> **Sent:** Tuesday, May 31, 2016 4:23 PM
> **To:** Robert Hammer; Maria Kempe; George Barany
> **Cc:** Pearson, Matthew; Valerie Cross; Monib Zirvi; Matthew Lubin; Brian Kelly
> **Subject:** Re: Privileged & Confidential: Cookies and Pie Analogy re: Status Report regarding Cornell University, et al. v. Illumina
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> Dear Rob, Maria, and George

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View less

--
George Barany
Distinguished McKnight University Professor of Chemistry
University of Minnesota
Department of Chemistry
[redacted]

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Date May 31, 2016 at 6:30 PM

Dear Maria, (George, Bob, Monib, and Matthew L.)

Good talking earlier today.

I think this is beautiful…

The food analogies will be used with the jury next year, so I agree we should think about this some more…

Valerie and I had a 2 hour discussion with Matthew P. today. Most of the writeup is very technical and legal, but Matthew said the email discussions back and forth — and especially Maria's diagrams and Henrik's movies were very helpful — preparing for our jury trial next summer.

Matthew still needs to get more work done and submit this June 2nd, so other than Henrik's "bonus" movie, and Maria's calculation on the total number of solid supports we covered in the patent — please email silence, no more responses for now.

Thank you all for your help with this.

All the best,

Francis

[redacted]
barany@med.cornell.edu

[redacted]

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Date Jun 1, 2016 at 9:07 AM

a few very quick notes

* adding my kudos to Maria and Henrik for this work

* with multiple movies (some in several iterations) it would be useful to have (in due course) a new self-consistent naming scheme, backed up by a simple chart that says which movie makes which point -- as FB already pointed out, no rush on this

* we invented PEG-PS, where a preformed PEG of defined length is covalently attached to preformed crosslinked polystyrene beads. this has been a highly successful commercial product. Independently, Rapp came up with something called Tentagel (or Rapp-resin) in which ethylene oxide is polymerized onto PS. Though the principle of how the materials are created is different, the final Tentagel product is very similar to PEG-PS

Good luck to the legal team in completing the various documents. I trust everything is under

control, but if you need to consult with me on anything or think it would be helpful for me to give things a final review, I am available today

things a final review, I am available today (Wednesday) starting late afternoon, and almost anytime tomorrow.

GB

View more

--
George Barany
Distinguished McKnight University Professor of Chemistry
University of Minnesota
Department of Chemistry
[redacted]

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Date Jun 1, 2016 at 1:00 PM

Dear All,

Please find attached a table with different combinations of substrates and surfaces. The table shows combinations of substrate + one surface. It is of course possible to add several surfaces to the substrate - those are not included in the table. All of the substrates in the table are listed in the patent. For the surfaces, I used the specific surfaces mentioned in the patent + materials belonging to the groups of materials listed in the patent (22:36-40). All entries marked with an "X" are those I believe are feasible and should be possible to do by those skilled in the art (=all=1254). I have entered some references to the patent - there are probably more missing, but at least it is a start.

I have a been thinking on the constructions by the judge:

(1) Immobilized was construed as "covalently bound" (or bound via hybridization)

(2) Attached was construed as covalently bound or **adsorbed**

(3) Starting at 22:29, the patent reads "Surfaces on the solid substrate will usually, though not always, be composed of the same material as the substrate. Thus, the surface may be composed of any of a wide variety of materials, for example, polymers, plastics, etc..." From this it is clear that the substrate

and the surface are two units (although they can be composed of the same type of material).

(4) 22:40 says: "The surface is functionalized with binding members which are attached firmly to the surface of the substrate." This means that the surface (for example a bead or a polymer layer) may be **adsorbed** [firmly] to the surface. Binding members does not need to be functional groups that bind by covalent bonds, but can be affinity ligands, hydrophobic groups that adsorbs to hydrophobic regions on the substrate, ionic groups that interact with ionic groups on the substrate etc. That leaves us with scenario D/E in the Master figure. Hence, the oligos are not covalently bound to the substrate (but rather covalently bound to the surface) according to the construction by the judge.

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Substrate & Surface combinations MK 1…

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Date Jun 1, 2016 at 1:59 PM

Dear Maria,

This is an awesome table.

Over the next few weeks, Bob, George, and yourself will list SOME of the composites, again, including the PEG-PS that George invented, and the Tentagel developed by Rapp and coworkers, to provide a deeper sense of the different combinations.

We should also remember to include examples of substrate + surface that could be used to make bead arrays. There are a number of ways to do so. For example, we could have etched glass as a first substrate, and silica or polystyrene beads as a second substrate. The beads would be functionalized by a silane surface. As another example, we could have etched glass as a first substrate, and then a composite of silane surface surrounding silica beads — that would be entered in the table as a composite surface. The word “bead”

should appear a number of times in the table, both under the potential to be used as surface and as the potential to be used as substrate

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Fantastic all around.

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Date Jun 2, 2016 at 8:07 AM

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Date Jun 2, 2016 at 8:08 AM

Pdf of the updated Master Figure A-F.

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Francis:

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As described in the patent, the solid-support can be made up of 18 different substrates in combination with 10 different surfaces containing appropriate functionality for chemistry required. For example the substrate could be a metal, such as aluminum, with a layer of polysaccharide (dextran) as the surface. This dextran surface is adhered to the substrate by non-covalent forces. The surface of dextran has hydroxyl groups that could used for attachment of the oligonucleotides by any variety of chemistries as described in the patent, including N,N'-carbonyldiimidazole. Another example could be an etched glass substrate in which a polymer coating of polyethylene acts as the surface. Again this polymer is adhered to the surface by non-covalent forces such as hydrophobic interactions. To create a better adherance, the substrate glass could be silanized with a hydrophobic group such dimethydichlorosilane. To provide functionality to the polyethylene surface one can oxidize the surface to produce carboxylate functionality which are readily activated to provide covalent attachment of oligonucleotides. For example the carboxylates are activated by a carbodiimide and an amine-functionalized is added to form an amide bond attachment. Another example could be a glass substrate. The surface could be provided by silica or polystyrene beads that are adhered to the surface non-covalently or covalently. For covalent attachment of the beads, one creates a composite bead by attaching a functionalized polymer coating such a polyethylene glycol to the bead. The resulting solid-support is a

combination of a glass surface with a composite bead attached to the glass. These techniques were well known to those skilled in the art at the time the patent was filed. As provided in the description, we provided 18 different surfaces with 10 different substrates to clearly provide at least 180 different composite solid-supports. More are possible as combinations of substrates and surface was described in the patent. So a substrate could be a glass substrate with a gold layer with a dextran layer added as the surface to make up the solid-support (REF from MARIA). The patent thus describes a wide range of combinations of materials that provide multilayered composite solid-supports, that in no way could be considered "single unitary substrates".

I have to go to some meetings this AM.

I will do more at lunch.

Bob

<Peanut_butter_on Toast1.jpg>

<Peanut_butter_on Toast2.jpg>

<Peanut_butter_jelly_on Toast3.jpeg>

<Peanut_butter_banana_on Toast4.jpg>

<Peanut_butter_banana_on Toast5.jpg>

<Peanut_butter_blueberries_on Toast6.jpg>

<Peanut_butter_mixed_berries_on Toast7.jpg>

<Peanut_butter_avacado_on Toast8.jpg>

<MK Food equivalencies 160531 .docx>

<ExtraMaterial.mov>

<Substrate & Surface combinations MK 160601.xlsx>

View less

Master Figure A-F.pdf.zip

Subject Re: Privileged & Confidential: Cookies and Pie Analogy re: Status Report regarding Cornell University, et al. v. Illumina

From Francis Barany <barany@med.cornell.edu>

To: Maria Kempe <maria.kempe@med.lu.se>

Cc: George Barany <barany@umn.edu>, Robert Hammer <rphammer@gmail.com>, Monib Zirvi <matzirvi@yahoo.com>, Matthew Lubin <lubingenetics@me.com>, Pearson, Matthew <mpearson@akingump.com>, Valerie Cross <vlc1@cornell.edu>, Brian Kelly <bjk44@cornell.edu>

Date Jun 2, 2016 at 8:20 AM

Dear Maria,

Well received, enclosed is the tiff version for insertion into a document.

Maria, when you get a chance, not critical now, kindly update the food analogy document to include Figure F — again, no need to have something symbolize the oligos, we just want people to understand that A, D, & E are equivalent, and B, C & F are equivalent.

Best,

Francis

[redacted]
[redacted]
barany@med.cornell.edu

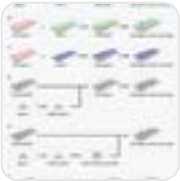
[redacted]

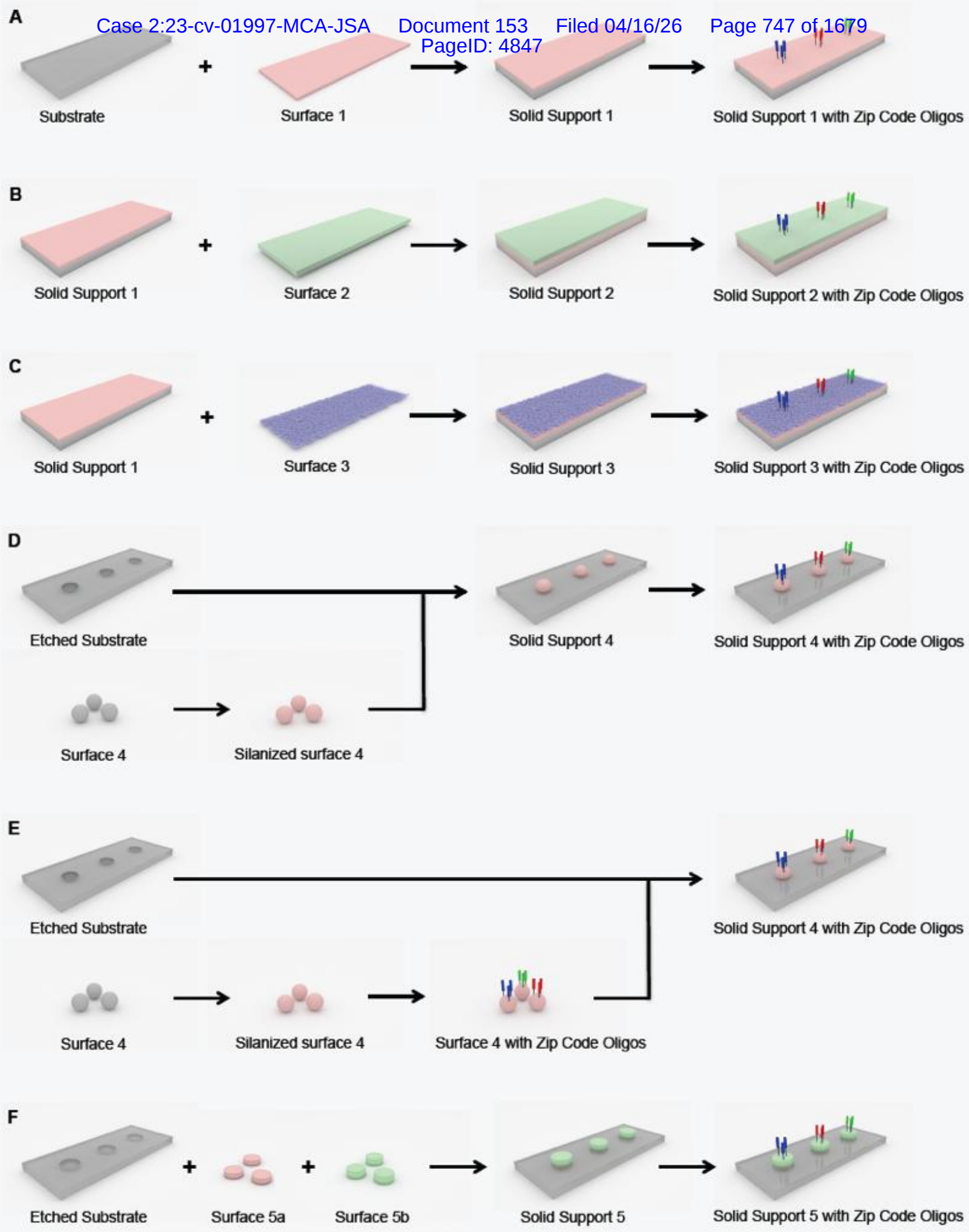
On Jun 2, 2016, at 8:04 AM, Maria Kempe
<maria.kempe@med.lu.se> wrote:

Dear All,

Please find an updated jpg of Master Figure A-F (with the new "bonus" figure F included). I will send a separate email with the pdf.

All the best,
Maria




A
Substrate
Surface 1
Solid Support 1
Solid Support 1 with Zip Code Oligos
B
Solid Support 1
Surface 2
Solid Support 2
Solid Support 2 with Zip Code Oligos
C
Solid Support 1
Surface 3
Solid Support 3
Solid Support 3 with Zip Code Oligos
D
Etched Substrate
Solid Support 4
Solid Support 4 with Zip Code Oligos
Surface 4
Silanized surface 4
E
Etched Substrate
Solid Support 4 with Zip Code Oligos
Surface 4
Silanized surface 4
Surface 4 with Zip Code Oligos
F
Etched Substrate
Surface 5a
Surface 5b
Solid Support 5
Solid Support 5 with Zip Code Oligos

Subject Privileged and Confidential: Analysis of random primer design and 50%-GC primer design for 20-mer arrays (Part 1)

From Francis Barany <barany@med.cornell.edu>

To: Pearson, Matthew <mpearson@akingump.com>, Valerie Cross <vlc1@cornell.edu>, Goldman Mike <Michael.Goldman@leclairryan.com>

Cc: Francis Barany <barany@med.cornell.edu>, Monib Zirvi <matzirvi@yahoo.com>

Date Jun 15, 2016 at 8:26 AM

Dear Matthew, Mike, and Valerie,

In the last 3 days, Monib and I have done the calculation on when does using random primer design (i.e. 20-mers, as per Wallace) run into trouble.

First, to help you visualize this, imagine all the ways you can make a 20-mer. Think of the zip codes as stars in a giant universe, where stars with similar sequences are near each other, and those with more dissimilar sequences are further away from each other. Once you choose a certain star, you cross out all it's nearest neighbors that differ by less than 25% sequence. Initially, every star you choose will cross out a large number of nearest neighbors, but after a while the "spheres of neighbors" start overlapping, and at some point, it becomes more difficult to find new stars that don't overlap.

Just to put things into perspective, you may remember in Sept. of 2015, Monib and I calculated of the 281 trillion 24-mer zip codes, how easy would it be to construct arrays that had 25% or greater mismatches, where the Tm values were in a nice

window, say between 70oC and 85oC. We recognized that half the sequences with GC content of 50% worked, and essentially all sequences with

of 50% worked, and essentially all sequences with GC content about 50% worked, so approximately 50% of the sequences remaining would work. Enclosed is the excel and pdf version of that analysis (v03)

Now, we repeated that analysis for all 20-mers, here, it's only 1.1 trillion 20-mer zip codes. Since now the question is what is the chance that the next zip code chosen will have 5 or more mismatches, you will notice that at 100,000 addresses, it's 96%, meaning that there is a 4% chance the very next one picked will have less than 5 mismatches. So roughly, at 100,000 zip codes of 20-mers, when choosing randomly (without regard to Tm) within the next 25 addresses chosen, at least one of them will have less than 5 mismatches with one of the previous ones. If we back off to 10,000 zip codes, the chances are about 0.4% (i.e. about 10-fold lower) that the very next one picked will have less than 5 mismatches. So roughly, at 10,000 zip codes of 20-mers, when choosing randomly (without regard to Tm) within the next 250 addresses chosen, at least one of them will have less than 5 mismatches with one of the previous ones. Enclosed is the excel and pdf version of that analysis (v04)

We can calculate the cumulative probability of running into trouble by doubling the number of addresses and seeing where the cross-over point is. When you look at the enclosed excel file, v05, we calculate the probability of from 16 to 19 matches (i.e. less than 25% mismatches) times the array size squared, divided by 2. An easy way to think about this is if we are comparing 100 addresses to each other, it's (100 x 99 comparisons) divided by 2. You compare each address to each other address, but then need to divide by 2 to avoid double counting. For 4096 address, we expect about 3 pair to have from 16 to 19 matches (i.e. less than 25% mismatches). As the array size doubles, the number of potential mismatches increases 4-fold — this makes intuitive sense since we are increasing the number of combinations by 2 squared = 4. You can see that at 262,000 addresses, already about 5% of zip codes have a pair, i.e. approximately 10% of the array would not work due to cross-

hybridization with other addresses. By 524,000 addresses, about 20% of the array would not work.

However, the original Wallace application did not say to use all 20-mers, it said to use random 20-mers with exactly 50% GC. If you take random 20-mers, and select out only the ones with GC content, you get about 17.6%. Monib took 30,000 random 20-mers, and selected only those with 50% GC = 5,282 the first time = 17.6%. Monib then ran a Monte-Carlo simulation to see how many 16 to 19 matches (i.e. less than 25% mismatches) he could find in the first 5,282. He got 7 pairs. He then repeated the analysis on another 30,0000 random sequences (this time he pulled out only 5,189 with exactly 50% GC) then did the Monte Carlo simulation on all 10,471, and found an additional 30 pairs = 37 in total. The number of problem pairs went from 7 to 37 which is 5.3 times higher when the array size doubled (instead of just 4 fold). Continuing this pattern for doubling array sizes leads to only 65% of the positions functioning for 167,000 and 7.6% functioning for 335,000. (See enclosed v08 — the macro files are two big to send via the Cornell server, so I will send separately via gmail…)

Matthew — important — would you kindly email to all how many addresses the largest Illumina arrays use right now? I know the infinium methylation 450K chip array uses at least 450,000 zip codes. I vaguely remember they have SNP infinitum arrays of over a million zip codes — please correct me if I am mistaken…

Hope this helps, please confirm that you were able to receive this and the next 3 emails — each containing individual files of about 10-17 MB.

Looking forward to our discussion tomorrow, best,

Francis

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

Zipcode_Cumulative_Probabilities_09_…

ATT00001.htm

Zipcode_Cumulative_Probabilities_06_…

ATT00002.htm

Zipcode_cumulative_error_random_arr…

ATT00003.htm

Zipcode_cumulative_error_random_arr…

ATT00004.htm

Zipcode_Cumulative_Probabilities_09_…

ATT00005.htm

Zipcode_Cumulative_Probabilities_06_…

ATT00006.htm

Zipcode_cumulative_error_random_arr…

ATT00007.htm

Zipcode_cumulative_error_random_arr…

ATT00008.htm

Subject Re: Privileged and Confidential: Analysis of random primer design and 50%-GC primer design for 20-mer arrays (Part 5)

From Francis Barany <barany@med.cornell.edu>

To: Pearson, Matthew <mpearson@akingump.com>, Valerie Cross <vlc1@cornell.edu>, Michael Goldman <Michael.Goldman@leclairryan.com>

Cc: Monib Zirvi <matzirvi@yahoo.com>, Francis Barany <barany@med.cornell.edu>

Date Jun 18, 2016 at 7:44 AM

Dear Matthew, (Mike, and Valerie),

Matthew, following up on our conversation on Thursday, I explained that the only thing missing from the analysis was the situation where two zip-code complements cross-hybridized with each other, thus effectively removing them from hybridizing to their appropriate address on the solid support.

Monib proceeded to make the reverse complement of each of the 10471 20-mer zip codes (with exactly 50% GC) and proceeded to compare them with the original zip code sequences. In other words, if a zip code complement had 16-19 matches with a zip code address on the solid support, then the first zip code complement would hybridize to the second zip code complement in solution.

We would predict that the calculation would yield about the same number of matches. The first calculation gave results for the initial 5,282 and 10,471 of 7 and 37 pairs with 16-19 matches (ratio of 5.3), while the second calculation gave results for the initial 5,282 and 10,471 of 10 and 42 pairs with 16-19 matches (ratio of 4.2). Averaging these

results (i.e. 17 and 79 respectively) gave a ratio of 4.647.

Thus, I redid the calculations for arrays of different sizes, and with an array of 167,536 address, the prediction is that 44% of the array would not work properly, while with 335,072 addresses, essentially the entire array would not work properly. However, we may have made an error in double counting the addresses (i.e. the numbers would be 22% and 51% respectively) — so please have someone independently derive the correct numbers using Monte Carlo simulations. In any case, it's quite clear that once the array gets beyond 100,000 addresses, a large portion of the array is not functioning correctly.

Matthew -- please confirm that you did receive this, that the reasoning is clear, and that you can communicate this to your computer expert such that he can do the Monte Carlo simulation directly to get exact numbers for arrays of 10,000, 20,000, 50,000, 100, 000, 250,000 and 500,000 addresses.

If your expert needs to speak with Monib or myself, let us know, but this should be pretty straightforward for a mathematician…

Looking forward to our discussion on June 27th.

All the best,

Francis

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

Zipcode_cumulative_error_random_arr…

ATT00001.htm

Zipcode_cumulative_error_random_arr…

ATT00002.htm

Subject Re: Privileged and Confidential: Initial Illumina Zip codes Part 1

From Francis Barany <barany@med.cornell.edu>

To: Pearson, Matthew <mpearson@akingump.com>, Valerie Cross <vlc1@cornell.edu>, Michael Goldman <Michael.Goldman@leclairryan.com>

Cc: Monib Zirvi <matzirvi@yahoo.com>, Francis Barany <barany@med.cornell.edu>

Date Jun 18, 2016 at 9:47 AM

Dear Matthew, Valerie, and Mike,

In Illumina's original "Decoding of Array Sensors with Microspheres" patent (US7033754_Chee_Czarnik_Stuelpnagel_2006.pdf, enclosed) they claim to have figured out how to decode 24-mers, and their first example is in using exactly 16 zip codes. (See 60172106 as originally filed 12_23_1999.pdf, also enclosed)

In their application US20030096239_Gunderson_Chee_Zip code_2003.pdf (enclosed in next email) they claim to have written a computer program to design their zip codes.

In figure 1, they write at the top "One method of generating sequences that meet the above requirements is to randomly generate sequences of given lengths and than (sp. should be then) pass these filters through a set of heuristic acceptance filters. In particular, the 24-mer Illumina Adapter sequences (IllumaCodes) were chosen as follows.
...

Then they have a box that says: "Decoder-Decoder Complementarity Score < 18", with the explanation:

A high decoder-decoder complementarity score indicates that the two decoders are likely to cross-hybridize in solution

hybridize in solution.

It appears to me that the cut-off of 18 is equivalent to “greater than 25% differences” between two 24-mer zip codes.

Matthew, if I understand correctly, by law, Illumina is obligated to turn over to you the source code not only of how they generated the zip code primers in the US20030096239_Gunderson_Chee_Zipcode_2003.pdf, but also any and all information on how they generated the 16 zip codes (and followup zip codes) that they claimed to have tested in the original US7033754_Chee_Czarnik_Stuelpnagel_2006.pdf patent.

So here are the questions:

1. Does the INITIAL computer program select for zip codes that have GC content of 50% and greater?

2. Does the INITAL computer program select for zip codes with a tight Tm range?

3. Does the INITIAL computer program select for zip codes that have either "25% or greater differences” or simply “greater than 25% differences”?

4. Does the INITIAL computer program select for zip codes that have either "25% or greater differences” or simply “greater than 25% differences” between one zip code sequence and the complement of another?

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The same questions should be asked about the US20030096239_Gunderson_Chee_Zipcode_2003.pdf computer program application — originally filed as a provisional on August 29, 2000. This is after

we submitted our own patent with the 4633 zip codes (US-US8492085_Zirvi_Barany_Zipcodes_2013_copy.pdf — in followup email) on April 14, 2000 — so we had clear priority in all these ideas, both in the original '917 patent, and also in the followup applications...

Matthew, we can discuss further on June 27th, but meanwhile, if the above evaluation of the source code from the INITIAL computer program has NOT been performed, I would appreciate it if it has been done. Likewise for the source code for the US20030096239 application.

Kindly confirm you did get this and followup (Part 2, Part 3) emails.

Best,

Francis

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

— — — — — — — — — — — — — —

Matthew and Valerie, you may not get the US20030096239_Gunderson_Chee_Zipcode_2003.pdf document (Part 2), but you can download directly from Google patents:

https://www.google.com/patents/US20030096239?dq=US20030096239+Gunderson&hl=en&sa=X&ved=0ahUKEwiA-ZbH2rHNAhXMeT4KHYifAUYQ6AEIHjAA

Matthew and Valerie, you may not get the US8492085_Zirvi_Barany_Zipcodes_2013_copy.pdf document (Part 3), but you can download directly from Google patents:

https://www.google.com/patents/US8492085?dq=US8492085+Barany&hl=en&sa=X&ved=0ahUKEwiTucOB2bHNAhWBXD4KHXpcA1kQ6AEIHDAA

EwjTdcCH2bFINAHWBXD4KHXpcATKQcALIHDAA

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Decoding_random_Zipcode_arrays_Gu…

ATT00001.htm

60172106 as originally filed 12_23_199…

ATT00002.htm

US7033754_Chee_Czarnik_Stuelpnag…

ATT00003.htm

Subject Re: Privileged and Confidential: Initial Illumina Zip codes Part 1

From Francis Barany <barany@med.cornell.edu>

To: Pearson, Matthew <mpearson@akingump.com>, Valerie Cross <vlc1@cornell.edu>, Michael Goldman <Michael.Goldman@leclairryan.com>

Cc: Monib Zirvi <matzirvi@yahoo.com>, Francis Barany <barany@med.cornell.edu>

Date Jun 18, 2016 at 9:47 AM

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...

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we submitted our own patent with the 4633 zip codes (US-US8492085_Zirvi_Barany_Zipcodes_2013_copy.pdf — in followup email) on April 14, 2000 — so we had clear priority in all these ideas, both in the original '917 patent, and also in the followup applications...

Matthew, we can discuss further on June 27th, but meanwhile, if the above evaluation of the source code from the INITIAL computer program has NOT been performed, I would appreciate it if it has been done. Likewise for the source code for the US20030096239 application.

Kindly confirm you did get this and followup (Part 2, Part 3) emails.

Best,

Francis

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

— — — — — — — — — — — — — —

Matthew and Valerie, you may not get the US20030096239_Gunderson_Chee_Zipcode_2003.pdf document (Part 2), but you can download directly from Google patents:

https://www.google.com/patents/US20030096239?dq=US20030096239+Gunderson&hl=en&sa=X&ved=0ahUKEwiA-ZbH2rHNAhXMeT4KHYifAUYQ6AEIHjAA

Matthew and Valerie, you may not get the US8492085_Zirvi_Barany_Zipcodes_2013_copy.pdf document (Part 3), but you can download directly from Google patents:

https://www.google.com/patents/US8492085?dq=US8492085+Barany&hl=en&sa=X&ved=0ahUKEwiTucOB2bHNAhWBXD4KHXpcA1kQ6AEIHDAA

EwjTdcCH2bFINAHWBXD4KHXpcATKQcALIHDAA

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Decoding_random_Zipcode_arrays_Gu…

ATT00001.htm

60172106 as originally filed 12_23_199…

ATT00002.htm

US7033754_Chee_Czarnik_Stuelpnag…

ATT00003.htm

Subject Re: Privileged and Confidential: Initial Illumina Zip codes Part 2

From Francis Barany <barany@med.cornell.edu>

To: Pearson, Matthew <mpearson@akingump.com>, Goldman Mike <Michael.Goldman@leclairryan.com>, Valerie Cross <vlc1@cornell.edu>

Cc: Monib Zirvi <matzirvi@yahoo.com>, Francis Barany <barany@med.cornell.edu>

Date Jun 18, 2016 at 9:48 AM

Francis

[redacted]

barany@med.cornell.edu

[redacted]

US20030096239_Gunderson_Chee_Zi…

ATT00001.htm

Subject Re: Privileged and Confidential: Initial Illumina Zip codes Part 3

From Francis Barany <francis.barany@gmail.com>

To: Pearson, Matthew <mpearson@akingump.com>, Valerie Cross <vlc1@cornell.edu>, Goldman Mike <Michael.Goldman@leclairryan.com>

Cc: Monib Zirvi <matzirvi@yahoo.com>, Francis Barany <barany@med.cornell.edu>

Date Jun 18, 2016 at 9:53 AM

Francis
Tel.# 212-746-6509 or 6507 or 6524
Fax.#212-746-8104
barany@med.cornell.edu
francis.barany@gmail.com

Cell# 917-957-3976

US8492085_Zirvi_Barany_Zipcodes_20…

Subject Re: Privileged and Confidential: Initial Illumina Zip codes Part 1

From Monib Zirvi <matzirvi@yahoo.com>

To: Francis Barany <barany@med.cornell.edu>

Cc: Pearson, Matthew <mpearson@akingump.com>, Valerie Cross <vlc1@cornell.edu>, Michael Goldman <Michael.Goldman@leclairryan.com>

Date Jun 18, 2016 at 10:48 AM

In addition, the software may have calculated a Tm...if the ranges that they were screening for were centered around 72 C that would be critical to know.

Monib

Sent from my iPhone

On Jun 18, 2016, at 9:47 AM, Francis Barany <barany@med.cornell.edu> wrote:

> Dear Matthew, Valerie, and Mike,
>
> In Illumina's original "Decoding of Array Sensors with Microspheres" patent (US7033754_Chee_Czarnik_Stuelpnagel_2006.pdf, enclosed) they claim to have figured out how to decode 24-mers, and their first example is in using exactly 16 zip codes. (See 60172106 as originally filed 12_23_1999.pdf, also enclosed)
>
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>
> requirements is to randomly generate sequences of given lengths and than (sp. should be then) pass these filters through a set of heuristic acceptance

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Kindly confirm you did get this and followup (Part 2, Part 3) emails.

Best,

Francis

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

— — — — — — — — — — — — — —

Matthew and Valerie, you may not get the US20030096239_Gunderson_Chee_Zipcode_2003.pdf document (Part 2), but you can download directly from Google patents:

https://www.google.com/patents/US20030096239?

dq=US20030096239+Gunderson&hl=en&sa=X&ved=0ahUKEwiA-ZbH2rHNAhXMeT4KHYifAUYQ6AEIHjAA

Matthew and Valerie, you may not get the US8492085_Zirvi_Barany_Zipcodes_2013_copy.pdf document (Part 3), but you can download directly from Google patents:

https://www.google.com/patents/US8492085?dq=US8492085+Barany&hl=en&sa=X&ved=0ahUKEwjTucOR2bHNAhWBXD4KHXpcA1kQ6AEIHDAA

———————————————

<Decoding_random_Zipcode_arrays_Gunderson_Illumina_2004 copy.pdf>
<60172106 as originally filed 12_23_1999.pdf>
<US7033754_Chee_Czarnik_Stuelpnagel_2006.pdf>

Subject Re: Privileged and Confidential: Initial Illumina Zip codes Part 1

From Francis Barany <barany@med.cornell.edu>

To: Monib Zirvi <matzirvi@yahoo.com>

Cc: Pearson, Matthew <mpearson@akingump.com>, Valerie Cross <vlc1@cornell.edu>, Michael Goldman <Michael.Goldman@leclairryan.com>

Date Jun 18, 2016 at 3:11 PM

Dear Monib,

In our original patent, we taught zip codes with Tm values in the range of 75oC to 85oC using the Tm = 4(G+C) + 2(A+T) calculations.

Subsequent programs (using Na+ at 1,000 mM, and Mg2+ at 0 mM) gave lower Tm calculations for our zip codes, in the range of about 75oC to 80oC. Please see enclosed excel file showing how 16 of our 465 addresses match 16 of their 3171 addresses, and how the next 100 or so of their addresses are in EXACTLY the same Tm range as our addresses - using the OligoAnalyzer 3.1 program from IDT:

https://www.idtdna.com/calc/analyzer

Other programs/parameters would give lower calculations, i.e. around 72.C — but that doesn't matter, the important point is that once they learned of the teachings of Barany, they could start with 16 of our zip-codes, and then run the computer program to mimic our teachings to make their next 3,154 sequences.

Hope this helps,

Francis

[redacted]

[redacted] [redacted]
barany@med.cornell.edu

[redacted]

US20030096239_Table 2_Compare_46…

ATT00001.htm

Subject Re: Priveleged and Confidential: Table 1, with 18 match = exactly 25% mismatches, & 8 duplicates

From Francis Barany <barany@med.cornell.edu>

To: Pearson, Matthew <mpearson@akingump.com>, Valerie Cross <vlc1@cornell.edu>, Goldman Mike <Michael.Goldman@leclairryan.com>

Cc: Monib Zirvi <matzirvi@yahoo.com>, Francis Barany <barany@med.cornell.edu>

Date Jun 20, 2016 at 9:04 AM

Dear Matthew, Valerie, Mike, and Monib,

Over the weekend, Monib and I did another set of analysis to better understand how much Illumina was following our teaching.

We started with Table 1 of the US20030096239 application (Gunderson & Chee, 2003), which had numbered up to 4,000 zip codes, but only had 3,978 listed. I went to Table to to find the 22 missing zip codes, as you well know by now, the first 16 were our zip codes (from our 465 or 4633 list). The other 6 missing zip codes were nothing special.

We then performed some analysis, looking at use of GC content, and looking at how many mismatches were actually present when comparing zip codes to each other.

First: GC content. The enclosed file, "Zip code final-3_Histograms_MZ_06_19_2016.xls" is a summary of that analysis. Monib calculated how many GC bases were in each 24-mer, and then determined the percent with 9, 10, 11, 12, 13, 14, 15, 16, 17, 18 etc. GC pairs. The blue color is the distribution from their list, the orange is the

distribution from our list, and the grey is the distribution you get with random 24-mer. Since we used tetramers that were on average higher in GC

used tetramers that were on average higher in GC content to generate our zip codes, unsurprisingly, our zip code distribution is shifted with a center around 14 GC bases, while Illumina's zip codes center around 13 bases — nevertheless, their distribution is closer to ours than to random.

More importantly, the vast majority of our zip codes have Tm values between 75oC and 80oC (using the IDT oligo analyzer 3.1 program with Na+ = 1000 mM, Mg2+ = 0 mM). Their zip codes have the IDENTICAL Tm distribution. If we look at the zip codes with the most divergent GC content (i.e. 10 or 11 GC, or 16 or 17 GC), both sets have a few outliers (i.e. 73-75oC on the low side, 80-82.9oC on the high side), but nothing extreme, more likely reflecting subtle differences in Tm calculation programs used by the different groups. Nevertheless, the concordance is unmistakeable, and it is clear they followed our teachings on designing the zip codes to have a tight Tm profile, in the range of about 75oC-80oC.

Second: Matches and mismatches. Monib did a comprehensive mismatch analysis between all 4,000 or their zip codes (as well as between our 4,633 zip codes). He did this in part to check how many times they had 17 or 18 matches. There were some examples of 17 matches. There were no examples of 19, 20, 21, 22, or 23 matches. Amazingly their zip codes 869 and 3774 had exactly 18 mismatches — this is in conflict with their claiming in Figure 1 that their computer program selected for "Decoder-Decoder Complementarity Score of < 18" (see enclosed). Their zip codes 869 and 3774 had a "Decoder-Decoder Complementarity Score "of EXACTLY 18. Thus, they lied. They did follow our teachings of 25% or greater mismatches, not their teachings of "Decoder-Decoder Complementarity Score of < 18" (i.e. greater than 25% mismatches).

(They also had 8 zip code pairs that were perfect 24 base matches, but that could be an internal control to show hybridization was unchanged by doubling the number of zip code beads. See the numbers below.)

(Our 4,633 zip codes gave many examples of 18 matches, as it should, given that we limited our design to combining tetramers that differed from each other by two bases, precisely to make sure we would have no more than 18 matches).

(When Monib did the analysis on 4,000 random sequences, he got the predicted distribution with a long tail, that included several examples of 17 and 18 matches, and 1 example of 19 matches).

Matthew, very important:

1. Has your computer person run the program to test how many examples of 17 or 18 (or greater) matches were present in the early Illumina arrays?

2. Has your computer person run the program to test how many examples of 17 or 18 (or greater) matches are present in the more recent Illumina arrays (Infinitum and Methylation)?

3. I understand they also use zip codes of 21-, 22-, and 23-mers in addition to a few 24-mers. Has your computer person run the program to test how many examples of 17 or 18 (or greater) matches are present in the slightly shorter zip codes, allowing for alignment were one or two bases overhangs on either side?

If not, would it be possible for him to complete that analysis soon? He can communicate with Monib on how to write the Macro in excel if needed, but honestly, this should be duck soup for any mathematician, and probably much better off running on a real computer rather than a desktop….

Looking forward to discussion next Monday.

Hope this helps, best,

Francis

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

Confirmed on 869 & 3774, see below

145 matches with 3893
178 matches with 3894
319 matches with 3908
432 matches with 3289
1767 matches with 3504
3050 matches with 3992
3174 matches with 3299
3341 matches with 3945

(2174 does not match — Monib meant 3174)

```
   869     AACAGTAGAGGCGAGGCCTGCGGG
3774     ACCCGTTAAGTCGACGCCTGCGGG
```

US20030096239_Table 1_plus22_A1_…

ATT00001.htm

Zip code final-3_Histograms_MZ_06_1…

ATT00002.htm ATT00003.htm

Subject Re: Priveleged and Confidential: Table 1, with 18 match = exactly 25% mismatches, & 8 duplicates

From Monib Zirvi <matzirvi@yahoo.com>

To: Francis Barany <barany@med.cornell.edu>

Cc: Pearson, Matthew <mpearson@akingump.com>, Valerie Cross <vlc1@cornell.edu>, Goldman Mike <Michael.Goldman@leclairryan.com>

Date Jun 20, 2016 at 9:11 AM

Yes I meant 3174. Sorry about the late night typo.

Monib

Sent from my iPhone

On Jun 20, 2016, at 9:03 AM, Francis Barany <barany@med.cornell.edu> wrote:

> Dear Matthew, Valerie, Mike, and Monib,
>
> Over the weekend, Monib and I did another set of analysis to better understand how much Illumina was following our teaching.
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(i.e. greater than 25% mismatches).

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```
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```

<US20030096239_Table 1_plus22_A1_Match_MZ_06_20_2016.xlsx>

<Zip code final-3_Histograms_MZ_06_19_2016.xls>

<US20030096239_Gunderson_Chee_Zipcode_2003_Fig1.tiff>

On Jun 19, 2016, at 11:48 PM, Monib Zirvi
<matzirvi@yahoo.com> wrote:

and 3908

On Sunday, June 19, 2016 11:47 PM, Monib Zirvi
<matzirvi@yahoo.com> wrote:

The sequences which matched at 18 positions are 869 and 3774.

The sequences which may have been duplicated are:
145
178
319
432
1767
3050
2174
3289
3299
3341
3504
3893
3894
3945
3992

Subject Re: Confidential Status Report regarding Cornell University, et al. v. Illumina

From Monib Zirvi <matzirvi@yahoo.com>

To: Pearson, Matthew <mpearson@AKINGUMP.com>

Date Jun 25, 2016 at 3:25 PM

Dear Matthew,

Sorry to bother you.
If you google these sequences:

TTGAAATCCAGCGCAAAATCTGCG

TGTCATGAATGATTGATCGCGCGA

They link our work in the 1990's to the only other places they reappear on the Internet a decade later. Google 's algorithms are designed to scour the entire internet for the authority on a given search. Hope this is helpful.

Have a great weekend.

Sincerely,

Monib Zirvi

Sent from my iPhone

On May 26, 2016, at 10:45 AM, Pearson, Matthew <mpearson@AKINGUMP.com> wrote:

I agree – the pictures look great

Thanks, everyone, for your thoughts and work on this.

From: Francis Barany [mailto:barany@med.cornell.edu]
Sent: Wednesday, May 25, 2016 3:21 PM

To: Maria Kempe
Cc: Pearson, Matthew; George Barany; Robert Hammer; Monib Zirvi; Valerie Cross; Matthew Lubin; Brian Kelly;

Zirvi, Valerie Cross, Matthew Lubin, Brian Kelly

Subject: Re: Confidential Status Report regarding Cornell University, et al. v. Illumina

Importance: High

Dear Maria,

Very creative! I'm hungry!

I defer to Matthew P.'s thoughts on how best to use these photos, and when it will have the greatest impact.

Yes, Fig. 1B looks correct as the final part of the process. Would you please send the powerpoint of the figure as I suggested, with Example A, B, and C, and the steps of combining substrate (glass in all cases, but Example 1B has dimples) with surface (polyethylene plate, silica beads, polymer), to create the solid support? Would you also please send the more complete powerpoint which includes the oligonucleotides?

When you get a chance, kindly label my slides 5 & 6 accordingly (glass, polymer — chemistry), etc.

Maria, the pictures are great, now we need to back it up to teach the judge that polymer = chemistry, and silica bead = chemistry.

With regards to the movie, please call my office and we can discuss...

Thanks!

Francis

Tel 212.746.6509 Office

[redacted]

barany@med.cornell.edu

[redacted]

We need to decide exactly which scenario we should show in the movie. So let's think about it...

Maria

On May 25, 2016, at 2:33 PM, Maria Kempe <maria.kempe@med.lu.se> wrote:

Dear All,

Please find attached some attempts to visualize one of the Cornell approaches vs the Illumina approach. Please also find a figure showing a slide with beads and oligos (for revision of Fig. 1B of my previously submitted comments). The latter figure was done by my brother Henrik. Please let me know if this is what you have in mind as the final product of Fig 1B. We can change it otherwise. Henrik can make a movie along these lines.

Best regards,
Maria

From: Francis Barany [barany@med.cornell.edu]
Sent: Wednesday, May 25, 2016 3:57 PM
To: Pearson, Matthew; Maria Kempe; George Barany; Robert Hammer
Cc: Monib Zirvi; Valerie Cross; Matthew Lubin; Brian Kelly; Francis Barany
Subject: Re: Confidential Status Report regarding Cornell University, et al. v. Illumina

Dear Bob, George, and Maria,

Just spoke with Bob. He reminded me that Maria should point out that use of glass, polystyrene, or silica beads are just another form of the "surface". He suggested labeling what "chemistry" the bead is made of — i.e. technically it is no different than our polymer surfaces. (See enclosed paper to see what chemistry Illumina is using, e.g. Silica — pg 875, I've also copied it for you below).

(Matthew P. — have they changed their bead chemistry to polystyrene? Independent of what their bead is made of, it is still the "surface", i.e. it has chemistry

Illumina is trying to argue that their glass wells are a first solid support, and the beads are a second solid support (not covalently attached). The oligo is attached covalently to a linker — but they claim the bead is a

covalently to a linker — but they claim the bead is a physical object, not a chemical.

What we need to explain is that in both cases the substrate is glass, the surface is chemistry. The surface can be either attached via covalent bonds to the substrate, or adsorbed to the substrate. The linker is chemistry that is part of the surface. The linker-surface can also be either attached via covalent bonds to the substrate, or adsorbed to the substrate. The oligonucleotide is then covalently attached to the linker.

(Maria, see Fig. 2B in the attached as an example of how the beads look when buried into the fiber-optic wells — you may use this as a guide for your drawing of "Example B")

Hope this clarifies…

Best,

Francis

[redacted]
barany@med.cornell.edu

[redacted]

Preparation of Oligonucleotide-Linked Beads and Bead Pools

A set of 1536 universal capture oligonucleotide sequences was synthesized. Each sequence was individually immobilized on activated beads, as follows, to create 1536 bead types. Silica beads ~3 µm in diameter (Bangs Laboratories, Inc.) were amino functionalized by incubation in 2.5% 3-amino-propyl-trimethoxysilane (Aldrich) in ethanol for 1 h at RT and then activated by reaction with 2% 2,4,6-trichloro-1,3,5-triazine (Aldrich) in acetonitrile for 2 h at room temperature. Synthetic oligonucleotides labeled at the 5 terminus with a primary amine were covalently attached to the activated beads by overnight reaction at 50°C in a solution of 3 M NaCl and 100 mM sodium carbonate (pH 11). All reagents were of highest purity

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<Cornell approach.jpg><Illumina approach.jpg><Slide with beads & oligos.jpg>

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Subject Privileged and confidential: who, how, when, and why slides

From Francis Barany <barany@med.cornell.edu>

To: Pearson, Matthew <mpearson@akingump.com>, Goldman Mike <Michael.Goldman@leclairryan.com>, Valerie Cross <vlc1@cornell.edu>

Cc: Monib Zirvi <matzirvi@yahoo.com>, Francis Barany <barany@med.cornell.edu>

Date Jul 6, 2016 at 8:58 AM

Dear Matthew, Mike, and Valerie,

Kindly find enclosed a set of slides that Monib and I put together which provides timelines and the direct evidence of who, how, when, and why they plagerized/stole Cornell IP.

More than one person has told me that what Illumina (Walt & Chee) did to Cornell (barany team) was worse than what Facebook (Zuckerberg) did to the Winklevoss twins.

I would also like to discuss how to best convey that Illumina tried to get inside information on this case when they gave me a supena with regards to the John Zebala case. They themselves directly tied the cases together. Valerie – would you please email a pdf of that supena to Mike, Matthew, and myself?

Matthew, you do have my questions from previously. While I understand answers to some questions may fall under the protective order, answers to others, such as the percentage of a randomly generate 20-mer array that would have more than 75% matches (at sizes of 10,000; 50,000; 250,000; 500,000; and 1,000,000) should be free and clear.

Matthew, do you have an expert mathematician, one who can do probabilities, but also explain very large

who can do probabilities, but also explain very large numbers in plain folksy language that jurists can understand?

Finally, Monib has organized “a few simple questions” – I am sure you’ve thought of all these, but the combined weight sure point to willful infringement.

I look forward to your thoughts and insights when we speak on July 8th.

Best,

Francis

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

Dear Francis,

I think asking a few simple questions out loud will clarify the important issues:

1. Are bead arrays, zip code arrays?

If they answer "No",

Then ask why the figures in their patent are labeled "Zip-code Array" and why zipcode, addressable, and universal are used without any appropriate explanation or definitions.

2. Do bead arrays have zip code sequences that target DNA to a location?

If they say order is "random",

Then ask do the beads switch positions once inserted in any given array.

Also how would you decode without knowing which sequence is targeted to which location?

3. Do the sequences used fit the '917 definitions for sets of zipcodes?

The lengths are 24 mer and then were changed to 20-24 mer. They all have Tm in a narrow range and it appears that software just picked sequences in the same 75-80 Tm range as taught by Barany '917. Also they claim >25% sequence differences when there is a pair that is exactly 25% different as elaborated in Barany '917

4. Did the key players know about Barany zip code patents and papers in 1999-2006?

There is a clear connection between original PPG and 465 zip code sequence list and the decoder pattent. When you google zip codes (i.e. TTGAAAAGCCTACACGACGGCGAA), why do they appear only in Barany work and the IP used to list sequence for bead array.

5. Did David Walt "steal" Barany ideas and intellectual property?

If they answer no,

What was David Walt working on before talking to Dr. Barany? Answer: creating artificial nose.

When did the first paper appear about using fiberoptic biosensors for DNA? Answer: 1996, a year after talking to Dr. Barany.

Were the original arrays "addressable"? Answer: no

When did "addressable" enter his papers? Answer: 1998

What makes them "addressable"? Answer: The use of zipcode DNA sequences

Is his "random" arrays a unique idea or "obvious"?

is his "random" arrays a unique idea or "obvious"?
Answer: the 96 set and the 465 set and the 4633 set of zipcodes are in a random order and represent different arrays and use zipcodes in different orders as well.

What "zipcode" sequences were used? Answer: eventually the zipcodes had the same length, Tm, and sequence differences and exact sequences he agreed he did not invent.

Monib

Cornell_Illumina_Case_Confidential_Su…

ATT00001.htm

Cornell_Illumina_Case_Confidential_Su…

ATT00002.htm

Subject Fwd: Cornell v. Illumina - Privileged Work Product

From Valerie Cross Dorn <vlc1@cornell.edu>

To: Monib Zirvi <matzirvi@yahoo.com>

Cc: Francis Barany <barany@med.cornell.edu>, Pearson, Matthew <mpearson@akingump.com>

Date Jul 10, 2016 at 1:56 PM

Monib, at the request of Francis, I am sending you our supplemental infringement contentions, due to be filed on Tuesday July 12.

Our contentions are redacted of information that Illumina has designated as confidential (primarily relating to Infinium chips). Appendix F, J, and M are not included because the claims from these patents about which we previously alleged infringement have been "selected out" of the suit (when we focused our claims to 30 at the direction of the court). In addition, you may notice that some of the patents are not in the charts (for example '474 and '477) - that is because no claims from those patents remain in suit so there is no point in talking about them (even though our position is that Illumina infringes them too).

I am collecting comments on the documents to deliver to Matt at Akin Gump by end of day Monday so he can factor in appropriate edits before the documents are finalized on Tuesday. I welcome your input.

Valerie Cross Dorn
Associate University Counsel
Cornell University
[redacted]

Begin forwarded message:

From: "Pearson, Matthew" <mpearson@akingump.com>

<mpearson@akingump.com>
Subject: Illumina - Privileged Work Product
Date: July 8, 2016 at 11:26:54 AM EDT
To: Valerie Cross Dorn <vlc1@cornell.edu>

Valerie –

I have attached REDACTED versions of infringement contentions.

2016-07-12 Supplemental Preliminary I…

ATT00001.htm

Redacted DRAFT 2016.06.17 Appx A - …

ATT00002.htm

Redacted DRAFT July 12 2016 Appx B …

ATT00003.htm

Redacted DRAFT July 12 2016 Appx C …

ATT00004.htm

Redacted DRAFT July 12 2016 Appx E …

ATT00005.htm

Redacted DRAFT July 12 2016 Appx G …

ATT00006.htm

Redacted DRAFT July 12 2016 Appx H …

ATT00007.htm

Redacted DRAFT July 12 2016 Appx I -…

ATT00008.htm

Redacted DRAFT July 12 2016 Appx K …

ATT00009.htm

Redacted DRAFT July 12 2016 Appx L -…

ATT00010.htm

Redacted DRAFT July 12 2016 Appx N …

ATT00011.htm

Redacted DRAFT July 12 2016 Appx O …

ATT00012.htm

Subject Re: Cornell v. Illumina - Privileged Work Product

From Monib Zirvi <matzirvi@yahoo.com>

To: Valerie Cross Dorn <vlc1@cornell.edu>

Cc: Francis Barany <barany@med.cornell.edu>, Pearson, Matthew <mpearson@akingump.com>

Date Jul 11, 2016 at 7:55 AM

The documents look great. One minor point is that I don't see mention of the their use of the word zipcode in their patents and patent applications. Specifically the bead arrays were referred to as a zip code array in some of their figures. This would make Illumicodes function exactly the same as Zipcodes. This is equivalent to them renaming Syntrix to Sentrix.

Sincerely,

Monib Zirvi

Sent from my iPhone

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Cornell University
[redacted]

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Subject: Illumina - Privileged Work Product
Date: July 8, 2016 at 11:26:54 AM EDT
To: Valerie Cross Dorn <vlc1@cornell.edu>

Valerie –

I have attached REDACTED versions of infringement contentions.

<2016-07-12 Supplemental Preliminary Infringement Contentions.docx>

Matthew A. Pearson
AKIN GUMP STRAUSS HAUER & FELD LLP
[redacted]

The information contained in this e-mail message is intended only for the personal and confidential use of the

recipient(s) named above. If you have received this communication in error, please notify us immediately by e-mail, and delete the original message.

<Redacted DRAFT 2016.06.17 Appx A - 470

Patent Infringement.docx>
<Redacted DRAFT July 12 2016 Appx B - 434
Patent Infringement.docx>
<Redacted DRAFT July 12 2016 Appx C - 039
Patent Infringement.docx>
<Redacted DRAFT July 12 2016 Appx E - 285
Patent Infringement.docx>
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Patent Infringement.docx>
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Patent Infringement.docx>
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Patent Infringement.docx>
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Patent_Infringement.docx>
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Patent Infringement.docx>
<Redacted DRAFT July 12 2016 Appx N - 016
Patent Infringement.docx>
<Redacted DRAFT July 12 2016 Appx O - 928
Patent Infringement.docx>

Subject Re: Cornell v. Illumina - Privileged Work Product / and Illumina response to Plaintiffs' objections re: Markman?

From Francis Barany <barany@med.cornell.edu>

To: Valerie Cross <vlc1@cornell.edu>, Pearson, Matthew <mpearson@akingump.com>

Cc: Monib Zirvi <matzirvi@yahoo.com>, Goldman Mike <Michael.Goldman@leclairryan.com>, Francis Barany <barany@med.cornell.edu>

Date Jul 11, 2016 at 1:45 PM

Dear Valerie & Matthew,

Following up on Monib's comment about Illumina using the term "Zip-code Array" in their own patent application, below are the figures from their own patent applications.

Given that they must have copied these from the Barany work, they must have been aware of our patents prior to the dates in the documents.

In addition to using our zip-code array term, they also use:

Zip = zip code sequence
U = Universal primer (we also use the term zip code primer)
Zip code = "Illumacode" (Gunderson and Chee, Figure 1 2003 application) and "IllumiCode" (Illumina product guide and Fan article.

In addition, Illumina makes a big deal about how the bead is not attached to the pore, and in their patent figures there is a very small space between them. This is totally misleading. I am enclosing Fig. 1

from both the Gunderson 2005 and the Chee 2004 bead decoding papers. In both cases it is quite clear the bead is securely embedded onto the

clear the bead is securely embedded onto the substrate to form the solid support.

Hope these figures help you — if not for the immediate deadline, then for the jury trial.

Valerie — Would you kindly email to Mike, Monib and myself the Illumina's response to our "Plaintiffs' Objections to the report and recommendations on claim construction" of magistrate judge Thynge? I vaguely remember that Illumina's response was due last week…

Most appreciated,

Francis

[redacted]
barany@med.cornell.edu

[redacted]

> On Jul 11, 2016, at 7:55 AM, Monib Zirvi <matzirvi@yahoo.com> wrote:
>
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>
> Sincerely,
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> Sent from my iPhone

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> Associate University Counsel
> Cornell University
> [redacted]
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> >
> > **From:** "Pearson, Matthew" <mpearson@akingump.com>
> > **Subject: Illumina - Privileged Work Product**
> > **Date:** July 8, 2016 at 11:26:54 AM EDT
> > **To:** Valerie Cross Dorn <vlc1@cornell.edu>
> >
> > Valerie –
> >
> > I have attached REDACTED versions of infringement contentions.

<2016-07-12 Supplemental Preliminary Infringement Contentions.docx>

Matthew A. Pearson

AKIN GUMP STRAUSS HAUER & FELD LLP

[redacted]

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<Redacted DRAFT 2016.06.17 Appx A - 470 Patent Infringement.docx>
<Redacted DRAFT July 12 2016 Appx B - 434 Patent Infringement.docx>
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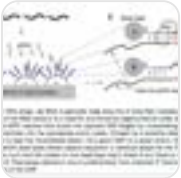
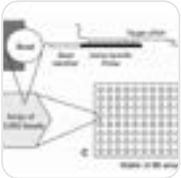
<Redacted DRAFT July 12 2016 Appx I - 746 Patent Infringement.docx>
<Redacted DRAFT July 12 2016 Appx K - 233 Patent_Infringement.docx>
<Redacted DRAFT July 12 2016 Appx L - 521 Patent Infringement.docx>

<Redacted DRAFT July 12 2016 Appx N - 016 Patent Infringement.docx>
<Redacted DRAFT July 12 2016 Appx O - 928 Patent Infringement.docx>

View less

Add universal PCR primers and PCR amplif
U2





Subject Privileged Communication: Sound Familiar?

From Francis Barany <barany@med.cornell.edu>

To: Pearson, Matthew <mpearson@AKINGUMP.com>, Valerie Cross <vlc1@cornell.edu>, Brian Kelly <bjk44@cornell.edu>

Cc: George Barany <barany@umn.edu>, Robert Hammer <rphammer@gmail.com>, Monib Zirvi <matzirvi@yahoo.com>, Francis Barany <barany@med.cornell.edu>

Date Jul 19, 2016 at 7:57 AM

Dear Matthew, Valerie, and Brian (and co-inventors),

I thought it all sounded a bit too familiar…see comparison below.

Matthew P., kindly let me know your schedule for a followup phone meeting… More helpful insights for you...

I will be away July 26th-29th and August 13th-29th.

Talk soon, all the best,

Francis

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

———————————————————

Ms. Trump, Monday night:

"From a young age, my parents impressed on me the **values that you work hard for what you want in life, that your word is your bond**

and you do what you say and keep your promise, that you treat people with respect. They taught and showed me values and morals in their daily lives. That is a lesson that I continue to pass along to our son. And we need to **pass those lessons on** to the many**generations** to follow. **Because we want our children in this nation to know that the only limit to your achievements is the strength of your dreams and your willingness to work for them.**"

Mrs. Obama, in her 2008 speech:

"Barack and I were raised with so many of the same **values: that you work hard for what you want in life; that your word is your bond and you do what you say** you're going to do; **that you treat people with** dignity and **respect,** even if you don't know them, and even if you don't agree with them. And Barack and I set out to build lives guided by these values, and **pass them on to the next generation**. **Because we want our children — and all children in this nation — to know that the only limit to** the height of **your achievements is the reach of your dreams and your willingness to work for them.**"

Ms. Trump:

"I was born in Slovenia, a small, beautiful and then-Communist country in Central Europe. My sister, Ines, who is an incredible woman and a friend, and I were raised by my wonderful parents. My elegant and hard-working mother, Amalija, introduced me to fashion and beauty. My father, Viktor, instilled in me a passion for business and travel. **Their integrity, compassion and intelligence reflects to this day on me and for my love of family and America.**"

Mrs. Obama, in 2008:

"And I come here as a daughter — raised on the South Side of Chicago by a father who was a blue-collar city worker and a mother who stayed at home with my brother and me. My mother's love has always been a sustaining force for our family, and one of my greatest joys is seeing her**integrity, her compassion and her intelligence reflected in my own daughters.**"

Michael Crowley
@michaelcrowley
in hindsight it did seem odd when Melania talked about the challenges of being a black woman at Princeton
7/19/16, 12:23 AM

Subject Re: Privileged Communication: Sound Familiar?

From Monib Zirvi <matzirvi@yahoo.com>

To: Francis Barany <barany@med.cornell.edu>

Cc: Pearson, Matthew <mpearson@AKINGUMP.com>, Valerie Cross <vlc1@cornell.edu>, Brian Kelly <bjk44@cornell.edu>, George Barany <barany@umn.edu>, Robert Hammer <rphammer@gmail.com>

Date Jul 19, 2016 at 2:03 PM

Thank you to the entire legal team for all of your hard work.
Dealing with infringement is as important as combatting plagiarism because it is protecting people's hard work.

Monib

"Plagiarism is a symptom of a broader culture, especially if it's not dealt with," says McBride. "How the culture responds to the act of plagiarism tells you a lot about that culture."

Sent from my iPhone

On Jul 19, 2016, at 7:57 AM, Francis Barany <barany@med.cornell.edu> wrote:

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>
> I thought it all sounded a bit too familiar…see comparison below.
>
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> insights for you...
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[redacted]

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[redacted]

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Subject Cornell Patent IPR status

From Weil, Jason <jweil@akingump.com>

To: barany@med.cornell.edu <barany@med.cornell.edu>, barany@umn.edu <barany@umn.edu>, maria.kempe@med.lu.se <maria.kempe@med.lu.se>, matzirvi@yahoo.com <matzirvi@yahoo.com>, rphammer@gmail.com <rphammer@gmail.com>, lubingenetics@me.com <lubingenetics@me.com>

Cc: vlc1@cornell.edu <vlc1@cornell.edu>, Pearson, Matthew <mpearson@AKINGUMP.com>

Date Aug 9, 2016 at 4:59 PM

All,

We wanted to give you all an update on the status of the patent office proceedings related to U.S. Patents Nos. 8,703,928 (the "'928 patent"), 8,288,521 (the "'521 patent"), 8,597,891 (the "'891 patent"), and 8,624,016 (the "'016 patent") (all Barany et al.).

As you know, in February, Illumina petitioned the patent office for inter partes review (IPR) of the above four patents related to arrays and LDR-PCR methods. In May we filed a preliminary response addressing the arguments in Illumina's petitions. Yesterday, the patent office denied Illumina's petitions for IPR of the '928,'521, '016 patents (the patents in the "array family"), but instituted IPR of the '891 patent (the patent in the LDR-PCR family).

For the '891 LDR-PCR patent, the Patent Office found, at this preliminary stage, that Illumina's submissions regarding the Zhang (1995) publication may establish it as prior art. The

Patent Office also found Zhang and combinations of Zhang and/or other references potentially sufficient to make claims of the '891 patent unpatentable as obvious. Those references

the '891 patent unpatentable as obvious. These references include: Chehab (1989), Tyagi (1994), Grossman (1994), and patents issued to Silver (1992), and Landegren (1991). The Patent Office's analysis is limited to evidence in the record at this preliminary stage, and we will have the opportunity to submit additional evidence during the course of the IPR.

We are currently reviewing the patent office's decision to institute IPR of the '891 patent to determine the best approach for the next steps in that proceeding. Our response to the petition is due November 8, and we plan to take the time necessary to carefully prepare that response.

We were very happy with the patent office's reasoning and analysis of the three array patents where our arguments carried the day. The infringement case for which you were all deposed will continue largely unaffected by yesterday's result. There will be no further proceeding on the three array patents in the patent office (unless Illumina seeks and prevails on a motion for rehearing, which is due in 30 days, on or before September 7). The claims of the '891 patent are not currently part of the selected claims in the infringement litigation, so the IPR will not delay our timeline to trial in July 2017.

We are happy to set up a call to answer any questions.

Thanks,
Jason

Jason Weil
AKIN GUMP STRAUSS HAUER & FELD LLP
[redacted]

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Subject Re: Analysts Pour Cold Water on Rumor of Thermo Fisher Making Acquisition Bid for Illumina

From Francis Barany <barany@med.cornell.edu>

To: bjk44@cornell.edu <bjk44@cornell.edu>, Valerie Cross-Dorn <vlc1@cornell.edu>, Goldman Mike <Michael.Goldman@leclairryan.com>, mpearson@akingump.com <mpearson@akingump.com>

Cc: Francis Barany <barany@med.cornell.edu>, George Barany <barany@umn.edu>, rphammer@gmail.com <rphammer@gmail.com>, matzirvi@yahoo.com <matzirvi@yahoo.com>

Date Aug 19, 2016 at 4:50 PM

Dear Brian, Valerie, Mike, and Matthew, et al.,

Greetings from Hungary, where I am with Isabelle (my oldest daughter) visiting relatives.

Just saw this below from GenomeWeb -- this is about as likely as Hillary choosing the Donald to be Secretary of State...

Your thoughts?

Best,

Francis

P.S. Cantor Fitzgerald is the brokerage firm that lost half their employees on 9/11.

Analysts Pour Cold Water on Rumor of Thermo Fisher Making Acquisition Bid for Illumina

Fisher Making Acquisition Bid for Illumina

Aug 18, 2016 | a GenomeWeb staff reporter

NEW YORK (GenomeWeb) – Following a report on Seeking Alpha that Thermo Fisher Scientific had made a $30 billion offer to acquire Illumina, a number of analysts said today that such a deal would be unlikely.

Both Thermo Fisher and Illumina declined to comment on the speculation.

In a research note, Cowen and Company analyst Doug Schenkel noted that such a deal would be "highly unlikely" for several reasons. The $30 billion offer would be less than a 20 percent premium to Illumina's stock price; a merger would raise antitrust issues; and such a deal would be difficult for Thermo Fisher to justify financially, Schenkel wrote.

Tim Evans, senior analyst with Wells Fargo, agreed that a deal would "encounter significant regulatory hurdles given that [Illumina] holds a near monopoly in high-throughput sequencing, and [Thermo Fisher] is the only current competitor with material scale in desktop sequencing."

Bryan Brokmeier, an analyst at Cantor Fitzgerald, added that Illumina would be unlikely to sell. Francis deSouza just took the reins as CEO of Illumina in July, he noted, and it would be surprising if he sold so quickly. In addition, he said, there is likely an "inflection point" in the clinical market that Illumina will recognize and that "isn't fully valued into the stock."

Thermo Fisher, meantime, would also be unlikely to want to acquire Illumina, Brokmeier wrote. Not only does the company have its own sequencing business, but it also recently acquired Affymetrix for $1.3 billion and is in the middle of a $4.2 billion acquisition of the microscope company, FEI Company.

Brokmeier noted that if Thermo Fisher does make an offer for Illumina, it could spur renewed interest in Pacific Biosciences by potential

interest in Pacific Biosciences by potential acquirers other than Roche, which has a partnership with PacBio, including PerkinElmer and Agilent Technologies.

In Thursday afternoon trade on the Nasdaq, shares of Illumina were up around 2 percent at $172.13 after climbing as high as $182.67 earlier in the day, while shares of Thermo Fisher were down around 1 percent at $153.29 on the New York Stock Exchange.

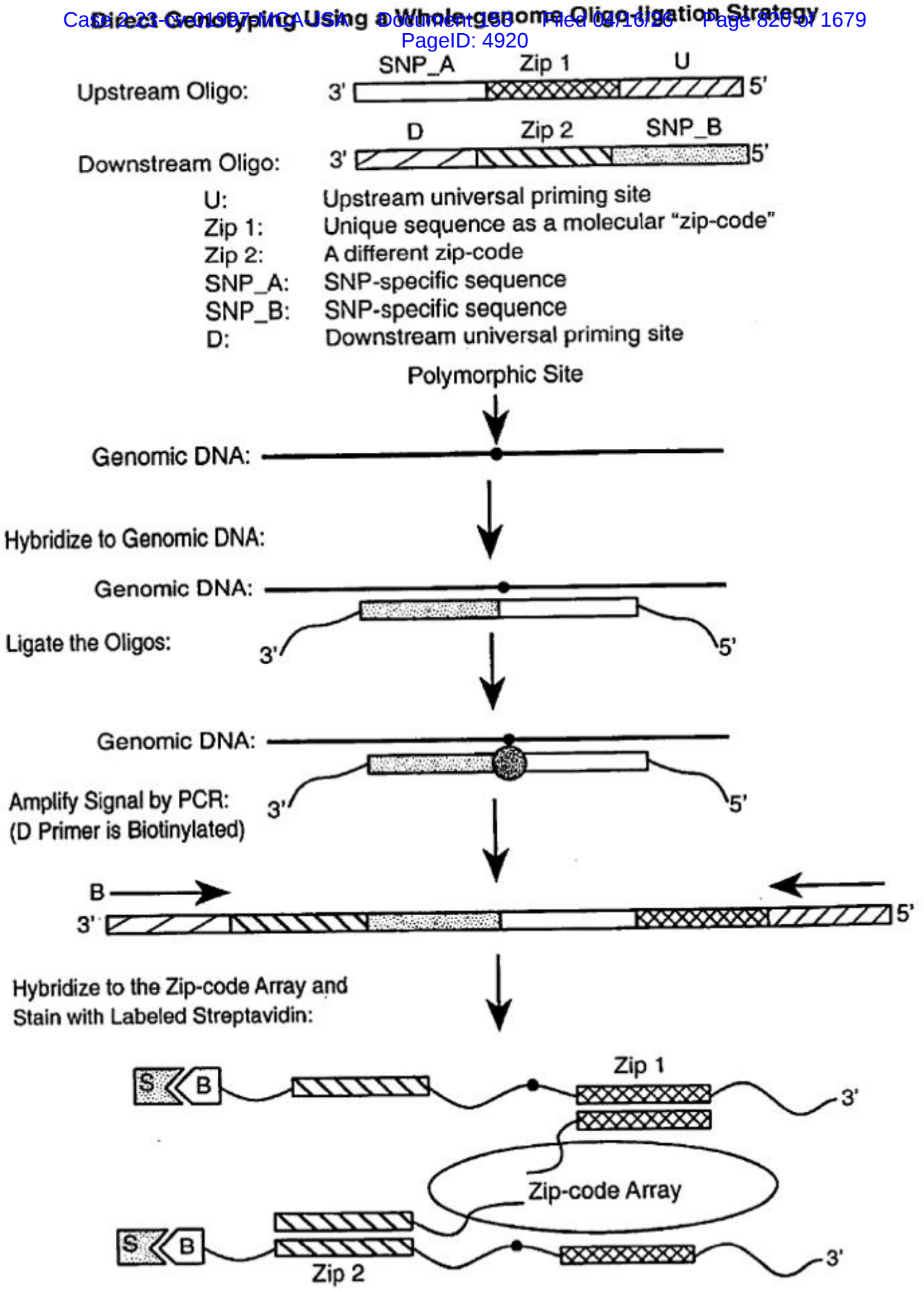
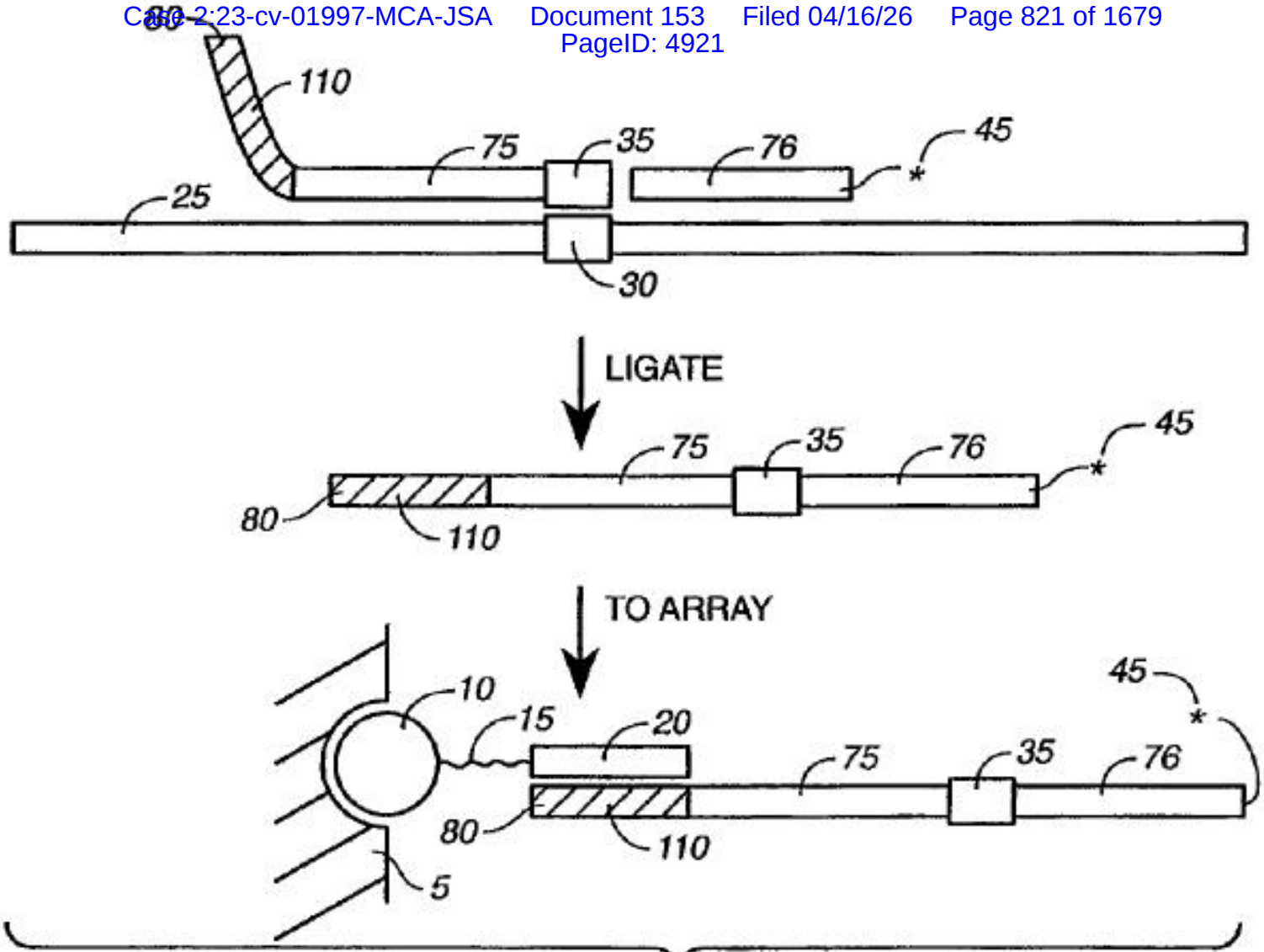

Direct Genotyping Using a Whole-genome Oligo-ligation Strategy
SNP_A
Zip 1
U
Upstream Oligo:
3'
5'
D
Zip 2
SNP_B
Downstream Oligo:
3'
5'
U: Upstream universal priming site
Zip 1: Unique sequence as a molecular "zip-code"
Zip 2: A different zip-code
SNP_A: SNP-specific sequence
SNP_B: SNP-specific sequence
D: Downstream universal priming site
Polymorphic Site
Genomic DNA:
Hybridize to Genomic DNA:
Genomic DNA:
Ligate the Oligos:
3'
5'
Genomic DNA:
Amplify Signal by PCR:
(D Primer is Biotinylated)
3'
5'
B
3'
5'
Hybridize to the Zip-code Array and
Stain with Labeled Streptavidin:
S
B
Zip 1
3'
Zip-code Array
S
B
Zip 2
3'

FIG._5


80
110
75
35
76
45
25
30
LIGATE
75
35
76
45
80
110
TO ARRAY
10
15
20
45
75
35
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80
110
5

FIG._10E

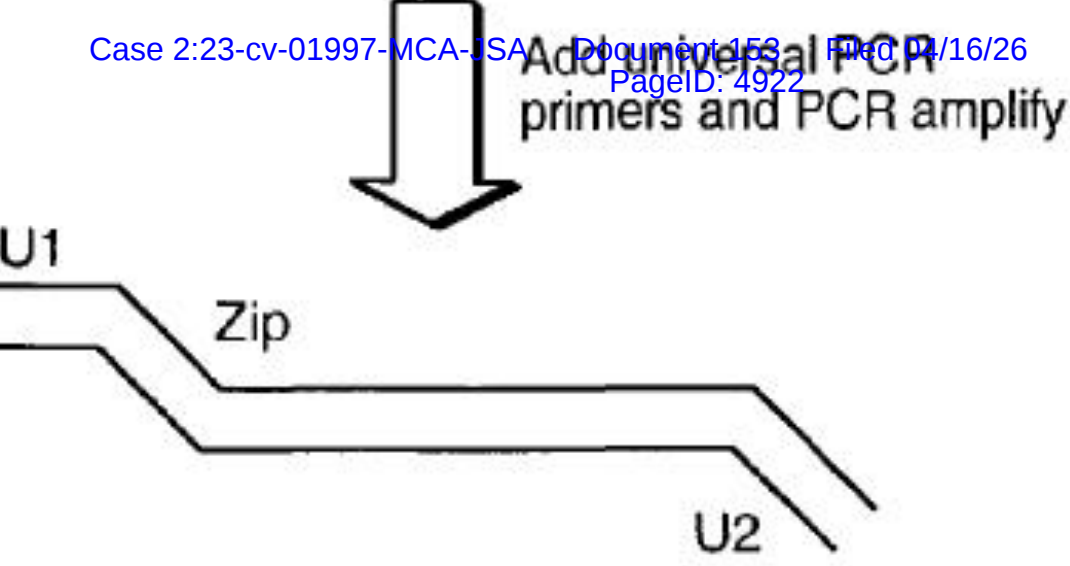


FIG._3

Description of algorithm to select "best" oligonucleotide adapter sequences.

Requirements for good sequences:

- Generates adequate hybridization signal intensity when employed in an experiment.
- Exhibits minimal cross-reactivity with other adapter sequences.
- Unique within the human genome sequence. This requirement can be extended to the genomic sequence of other organisms such as the fruit fly, the mouse, etc.

One method of generating sequences that meet the above requirements is to randomly generate sequences of given lengths and than pass these filters through a set of heuristic acceptance filters. In particular, the 24-mer Illumina Adapter sequences (IllumaCodes) were chosen as follows.

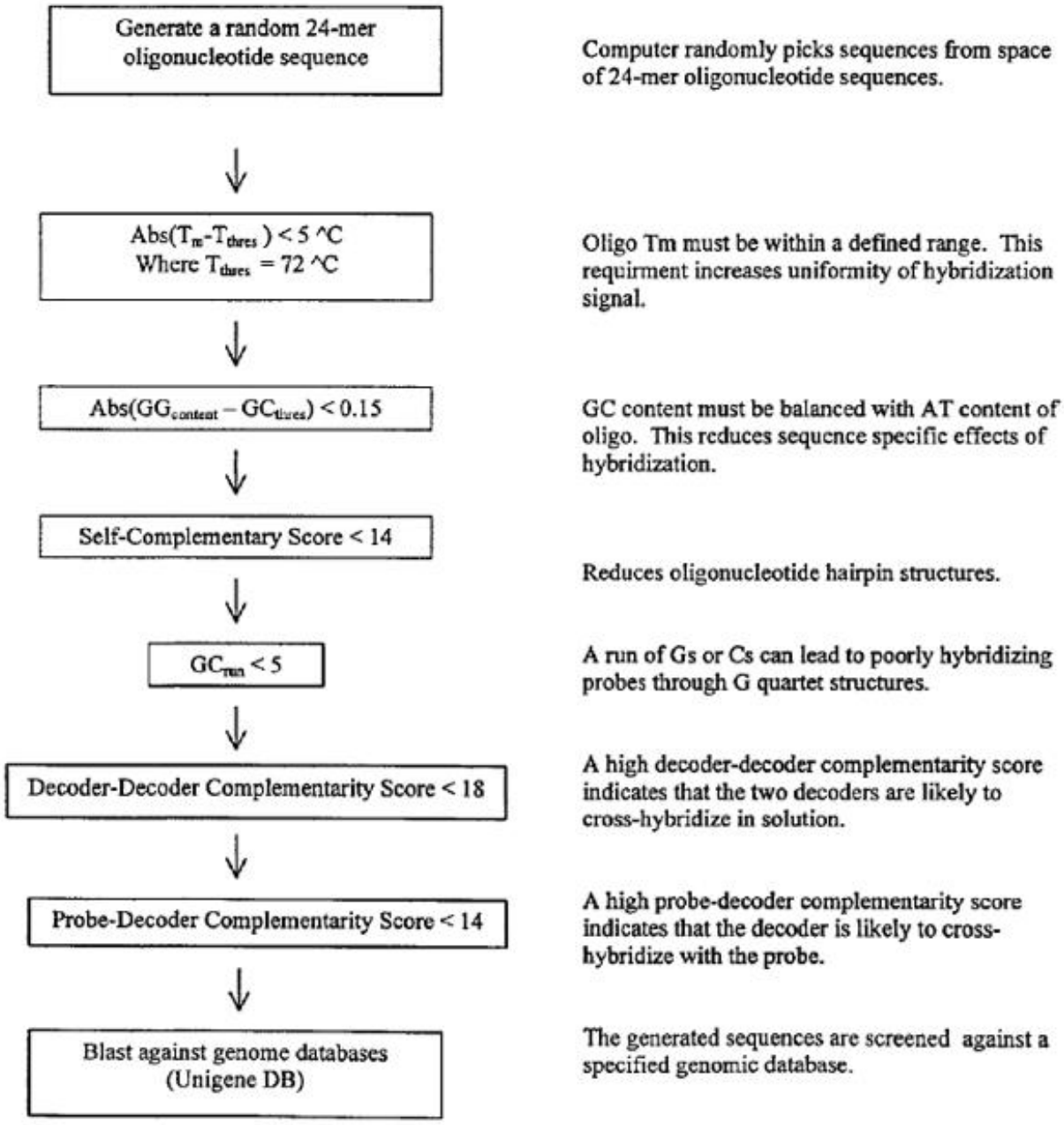


FIGURE 1

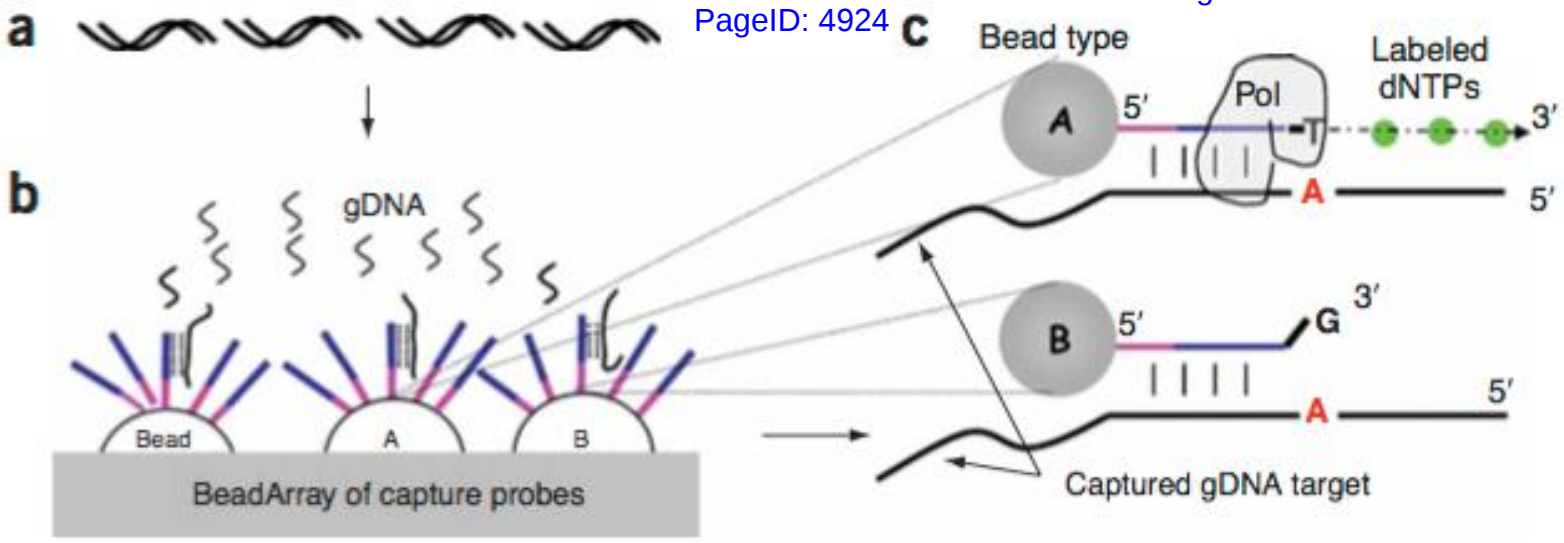
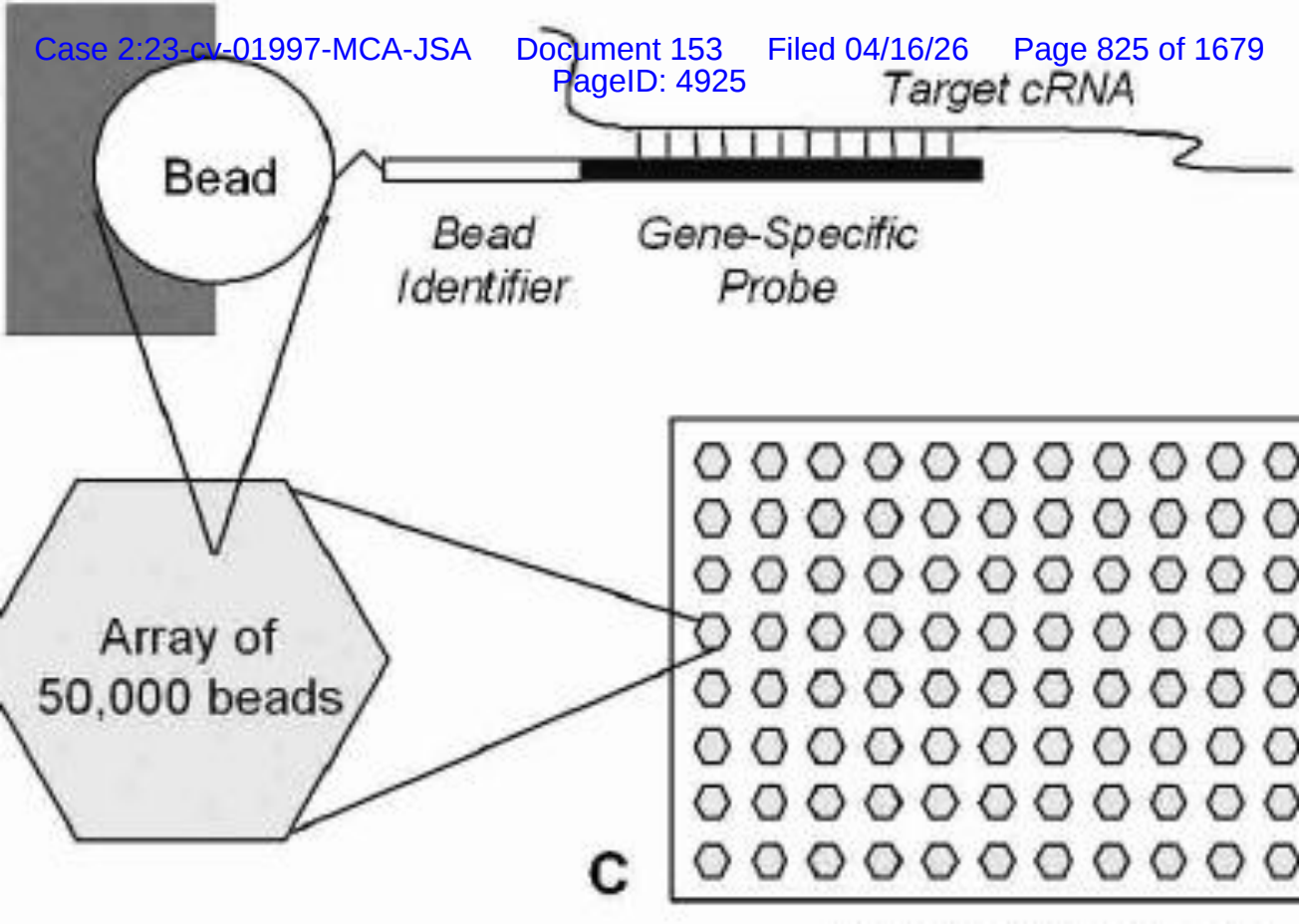


Figure 1 WGG on DNA arrays. (**a**) WGA to generate large amounts of amplified complex gDNA. (**b**) Hybridization of the WGA product to a specific and sensitive oligonucleotide probe array (50-mers). (**c**) An array-based ASPE reaction that scores the captured SNP targets by incorporating multiple biotin-labeled dNTP nucleotides into the appropriate allelic probe, followed by a sensitive detection and signal amplification step to read the incorporated labels. For a given SNP on a given strand, ASPE uses two different allele-specific bead types whose capture sequence is identical except for the 3′ terminal base. The base is chosen such that the probes on one bead type match allele A and those on the other bead type match allele B. Polymerase extension occurs preferentially from matched 3′ termini, enabling appropriate scoring of the SNP.


Target cRNA
Bead
Bead Identifier
Gene-Specific Probe
Array of 50,000 beads
C

Subject RE: Privileged and Confidential: Figure 21f from '917 for Markman II and "coupled to"

From Pearson, Matthew <mpearson@AKINGUMP.com>

To: Francis Barany <barany@med.cornell.edu>, Weil, Jason <jweil@akingump.com>, Valerie Cross <vlc1@cornell.edu>

Cc: Monib Zirvi <matzirvi@yahoo.com>

Date Nov 22, 2016 at 9:56 AM

Received - thanks

From: Francis Barany [mailto:barany@med.cornell.edu]
Sent: Tuesday, November 22, 2016 9:55 AM
To: Pearson, Matthew; Weil, Jason; Valerie Cross
Cc: Monib Zirvi; Francis Barany
Subject: Re: Privileged and Confidential: Figure 21f from '917 for Markman II and "coupled to"
Importance: High

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and being capable of hybridizing under uniform conditions, and if it is capable of being used as such, i.e. by hybridizing complementary sequences to those addresses, with minimal cross-hybridization, then it qualifies as a zip code array. Period. It does not matter what other sequences, naturally occurring, or other sequences, are on the array, nor does not matter if certain products hybridize to those sequences or not, as long as the assay is designed correctly, as any POSA would be able to do by following the teachings of Barany.

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From the '917 specifications, Fig. 13:

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Subject Re: Privileged and Confidential: Corrected powerpoint, includes updates re: Fig.21 & capturing on a solid support

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Cc: Valerie Cross <vlc1@cornell.edu>, Monib Zirvi <matzirvi@yahoo.com>, Francis Barany <barany@med.cornell.edu>

Date Nov 28, 2016 at 9:46 AM

Dear Matthew,

Over the weekend, I was preparing two PowerPoint documents for Mike Goldman re: Illumina's attempt to overturn the claims of '269 & '373, since they are violating our claims with regards to their sequencing products.

In the process of making the figures, I realized to my embarrassment that I had mislabeled directionality in some strands in the figures I sent you (i.e. 3' to 5', when it should have been 5'-3') and further, that I had flipped the orientation of some of the PCR primers. While technically correct, it didn't mesh with the way I drew them in the original patent filings, and as such, could confuse a jury.

I corrected them, and also included the drawings and explanations of Figure 21F and Figure 7 top of array.

In order to simplify, I put all the drawings, as well as the key comments into a single powerpoint document for you to have during your Markman presentation. I made a few subtle corrections, so please take a look. I am sending in both powerpoint

and pdf versions, so you can make your own changes, and have a printout with you at the hearing

hearing.

Would you please also forward this to Dianne Elderkin as well?

Most appreciated, and good luck tomorrow!

All the best,

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barany@med.cornell.edu

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Comments_Zip_code_array_variations_…

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Subject Privileged

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To: George Barany <barany@umn.edu>, Robert Hammer <rphammer@gmail.com>, Maria Kempe <maria.kempe@med.lu.se>, Matthew Lubin <lubingenetics@me.com>, Monib Zirvi <matzirvi@yahoo.com>

Cc: Francis Barany (barany@med.cornell.edu) <barany@med.cornell.edu>, Valerie Cross Dorn <vlc1@cornell.edu>

Date Dec 13, 2016 at 4:01 PM

Privileged

Dear all –

I have attached a summary of a hearing that we had with the court on November 29 in the case against Illumina. Please let us know if you have any questions.

Best,
Matt Pearson

Matthew A. Pearson
AKIN GUMP STRAUSS HAUER & FELD LLP
[redacted] 19103-7013 | USA | Direct: +1 215.965.1258 | Internal: 21258
Fax: +1 215.965.1210 | mpearson@akingump.com | akingump.com | Bio

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Memo to Inventors re 11-29-2016 heari…

Akin Gump
STRAUSS HAUER & FELD LLP

M E M O R A N D U M

ATTORNEY-CLIENT PRIVILEGED

December 13, 2016

To: Francis Barany and Coinventors

From: Akin Gump

Re: November 29, 2016 Hearing

On November 29, 2016, the Parties appeared before Judge Stark to address their Objections to the Report and Recommendations on Claim Construction issued by Magistrate Judge Thynge, as well as Illumina's Motion to Amend its Answer to plead inequitable conduct.

The majority of the argument focused on claim construction issues. In particular, the parties addressed three terms or groups of terms at issue in the litigation:

1. **Solid Support/Linker**

[redacted]

[redacted]

[redacted]

[redacted]

2. Capture Oligonucleotide

[redacted]

[redacted]

[redacted]

[redacted]

3. The 25% Difference Terms

[redacted]

[redacted]

[redacted]

<u>Motion to Amend</u>

Finally, the parties addressed Illumina's Motion to Amend to plead inequitable conduct as a defense. The focus of the defense here being a statement that was made during prosecution that contends the inventions were conceived and reduced to practice prior to June 22, 1994. Magistrate Judge Thynge previously determined that one could plausibly infer from the facts submitted by Illumina that this was a false statement and that the patent applicants made the statement with the intent to deceive the Patent Office. Plaintiffs' argued that the intent to deceive must be more than plausible, and that there was evidence of candor and good faith that should preclude a defense of inequitable conduct. Specifically, Plaintiffs' argued that deceptive intent must be the single most reasonable inference that can be drawn from the facts plead, but Illumina's pleading leads to several possible inferences. The Court questioned whether it was enough to plead such facts because they must be taken as true at this stage, but Plaintiffs explained that it is not enough to point to a statement that may be untrue and argue there is deceptive intent, there must be some evidence to support the assertion of intent as well.

Illumina argued the pleading standard only required Illumina to show that one could reasonably infer deceptive intent from the facts alleged, not that the single most reasonable inference was deceptive intent. The Court questioned whether the facts alleged led to an inference of deceptive intent if one could read the statements made in prosecution to mean that conception occurred by June 22, 1994 and the invention was diligently reduced to practice thereafter. The Court also expressed some concern that Illumina's entire inequitable conduct argument rested on a single sentence that Illumina acknowledged is inartfully written, and that such a threadbare accusation might not be what the Federal Circuit had in mind in its *Exergen* opinion.

The Court asked Illumina whether they could bring any additional evidence to bear if he allowed them to plead the inequitable conduct defense. Illumina responded that it could present a legal expert to describe patent practice and the MPEP requirements to support its claim, along with cross-examination of the relevant parties.

There was also some discussion regarding the standard of review that should be applied by Judge Stark in reviewing Judge Thynge's recommendation on this issue. Plaintiffs contend a *de novo* review applies, while Illumina argued in favor of review for clear error.

We have no control over when the Court will make a decision on the issues it heard, but we continue to prepare for the trial (scheduled to begin on July 10, 2017). We do not anticipate the need for the inventors to do anything case-related over the holidays, but we will follow up with appropriate individuals in the new year as needs arise during our pre-trial preparation.

Subject Re: Privileged

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Date Dec 13, 2016 at 4:53 PM

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1. Should “I” take off a week (or more) for the July 10th trial?

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Date Dec 15, 2016 at 8:04 AM

Dear all -

These are certainly reasonable questions. The timing of these decisions and arrangements will start after the new year. And no one would need to make travel or hotel arrangements on their own.

Best,
Matt

Sent from my iPhone

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[redacted]

On Dec 13, 2016, at 4:01 PM, Pearson, Matthew <mpearson@AKINGUMP.com> wrote:

Privileged

Dear all –

I have attached a summary of a hearing that we had with the court on November 29 in the case against Illumina. Please let us know if you have any questions.

Best,
Matt Pearson

Matthew A. Pearson
AKIN GUMP STRAUSS HAUER & FELD LLP
[redacted]

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<Memo to Inventors re 11-29-2016 hearing.pdf>

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Subject Re: Privileged

From Monib Zirvi <matzirvi@yahoo.com>

To: Pearson, Matthew <mpearson@AKINGUMP.com>

Date Dec 15, 2016 at 8:09 AM

Thank you.

Monib Zirvi

Sent from my iPhone

On Dec 15, 2016, at 8:04 AM, Pearson, Matthew <mpearson@AKINGUMP.com> wrote:

Dear all -

These are certainly reasonable questions. The timing of these decisions and arrangements will start after the new year. And no one would need to make travel or hotel arrangements on their own.

Best,
Matt

Sent from my iPhone

On Dec 13, 2016, at 4:53 PM, Francis Barany <barany@med.cornell.edu> wrote:

> Dear Matthew and Jason,
>
> Two questions that has been sent to me concerning our availability for the July 10th trial — understood the answer may be different for each of us..
>
> 1. Should “I” take off a week (or more) for the July 10th trial?
>
> 2. When will we need to book rooms for the trial in Wilmington Delaware?

Sorry, we do not have the experience in this that you have.

Thanks,

Francis

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

On Dec 13, 2016, at 4:01 PM, Pearson, Matthew <mpearson@AKINGUMP.com> wrote:

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Matthew A. Pearson
AKIN GUMP STRAUSS HAUER & FELD LLP
[redacted]
[redacted] 19103-7013 | USA | Direct: +1 215.965.1258 | Internal: 21258
Fax: +1 215.965.1210 | mpearson@akingump.com | akingump.com | Bio

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<Memo to Inventors re 11-29-2016 hearing.pdf>

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View less

Subject Privileged and Confidential: Detailed Case Summary and Strategic Alignment: Cornell and Akin Gump Only; Parts 2 & 3

From Francis Barany <barany@med.cornell.edu>

To: Valerie Cross <vlc1@cornell.edu>, Pearson, Matthew <mpearson@AKINGUMP.com>, Weil, Jason <jweil@akingump.com>

Cc: Dianne Elderkin <delderkin@akingump.com>, Gary Koretzky <gak2008@med.cornell.edu>, Carl F. Nathan <cnathan@med.cornell.edu>, Brian Kelly <bjk44@cornell.edu>, Monib Zirvi <matzirvi@yahoo.com>, Francis Barany <barany@med.cornell.edu>

Date Dec 19, 2016 at 3:05 PM

Francis

[redacted]

barany@med.cornell.edu

[redacted]

Cornell_Illumina_Case_Confidential_Su…

Cornell_Illumina_Case_Confidential_Su…

Subject Privileged and Confidential: Detailed Case Summary and Strategic Alignment: Cornell and Akin Gump Only; Part 1

From Francis Barany <barany@med.cornell.edu>

To: Valerie Cross <vlc1@cornell.edu>, Pearson, Matthew <mpearson@AKINGUMP.com>, Weil, Jason <jweil@akingump.com>

Cc: Dianne Elderkin <delderkin@akingump.com>, Gary Koretzky <gak2008@med.cornell.edu>, Carl F. Nathan <cnathan@med.cornell.edu>, Brian Kelly <bjk44@cornell.edu>, Monib Zirvi <matzirvi@yahoo.com>, Francis Barany <barany@med.cornell.edu>

Date Dec 19, 2016 at 3:06 PM

Dear Valerie, Matthew, and Jason,

Over the past few weeks, Monib Zirvi and I have uncovered some additional damning evidence by scouring SEC 10K-405 and 10Q reports. Over the weekend, Monib and I continued to refine the overall document.

In this and followup emails, kindly find enclosed pdfs in 9 parts providing the detailed summary of the case and draft strategy for moving forward. This document has been substantially revamped since I shared it with the Cornell team in July of 2016.

This document is for Cornell and Akin Gump ONLY. I enclose the revised Executive Summary below.

I do hope you will have time to review the document in its entirety, but if not, please look at Part 4, pages

65-91, with the updated timeline and evidence of outright plagiarism of our zip codes, as well as Illumina knowingly and willfully infringing on Cornell

Illumina knowingly and willfully infringing on Cornell IP.

Part 8, pages 162-167 uncovers details in the Joint Collaboration Agreement that I am sure Matthew knew about under the protective order, but thanks to the extraordinary increased power of the Google search engine in just the last few years, we found it anyway in public SEC filings.

Finally, Part 9, pages 168-184 provide a summary of the detailed timeline, Illumina's plagiarizing our patented ideas, zip codes, and figures, as well as an overall storyline in plain non-technical language, and a "jury friendly" approach to guide a fair damages award or settlement to Cornell and ABI.

While the overall picture is now quite clear, there are still pieces of the puzzle that are missing (at least to the inventors, it may already be uncovered within the protective order), and I would like to ask some questions about this, but not appropriate for email.

Looking forward to our webex discussion on January 10th.

Wishing you a peaceful holiday season.

Best,
Francis

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

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Cornell_Illumina_Case_Confidential_Su…

Executive Summary

1. In 1994-1996 the Barany lab developed and patented "Zip code chemistry" and "Addressable Arrays", IP that became the foundation of modern day commercial tests to diagnose and identify disease using DNA arrays and Next-gen sequencing (NGS), and they have generated an estimated $7 billion in revenue to other parties. One can think of zip code chemistry as the original Microsoft operating system (MS-DOS), and PCR-PCR-LDR, or LDR-PCR as applications, like email and text messaging.

2. Our patents are licensed to Applied Biosystems Inc. (ABI, now Thermo Fisher), which signed a Joint Development Agreement with Illumina in November 1999 to develop our LDR and Addressable Array patents. The collaboration between ABI and Illumina dissolved acrimoniously in 2002 without commercializing any products at that time, but Illumina kept using Cornell patents without a license.

3. Both ABI and Illumina have independently commercialized many products using Cornell patents since that time, but only ABI has a license. ABI & Cornell sued Illumina in 2010 for violation of the subset of patents involving array technology, but did not include the sequencing patents in the suit. ABI & Cornell have retained Akin Gump, with Matthew Pearson and Dianne Elderkin, best known for having won the $1.7 B award on Humira and Remicade infringement of NYU's IP.

4. Illumina is fighting back – filing four "Petitions for Inter Partes Review" (IPR's), and two "Petitions for Ex Partes Review" trying to invalidate our *DNA array and sequencing patent claims*. Since the facts are in Cornell's favor, Illumina's overall strategy is to malign the reputation of the inventors, lawyers, and Cornell. Cornell is now winning in *all* 6 of these cases.

5. Dr. Barany has found four "smoking guns" that prove our case and provide overwhelming evidence of willful infringement. Among these are evidence that competing IP never worked, that Illumina failed to commercialize 7 of their own IP to decode beads, that employees of Illumina plagiarized Barany zip codes and intellectual property, and Illumina knowingly and willfully tried to conceal their infringement. Illumina knowingly copied the "look and feel" of Addressable Arrays in the Barany patents – just as Samsung copied Apple. Further, imagine if Samsung had used the word "iPhone" in their patents with no explanation.

6. Over 90% of Illumina products, to this day, would not be possible without using Barany/Cornell IP. It is fair to conclude that without access to, and use of the ideas and know-how in Barany/Cornell IP, Illumina would not exist in its current form.

7. Drs. Barany and Zirvi have provided an overall storyline and summary of the case in plain non-technical language, and have developed a "jury friendly" approach to guide a fair damages award or settlement to Cornell and ABI.

Cornell – Illumina Case
Privileged and Confidential
Cornell and Akin Gump Lawyers Only

Jackson Pollock Number 17A 1948

Executive Summary

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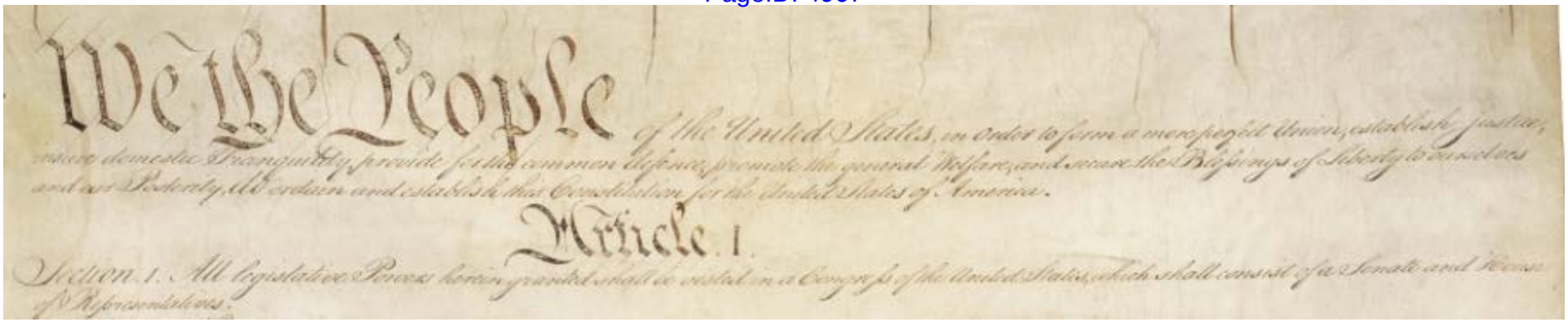
Cornell – Illumina Case Background

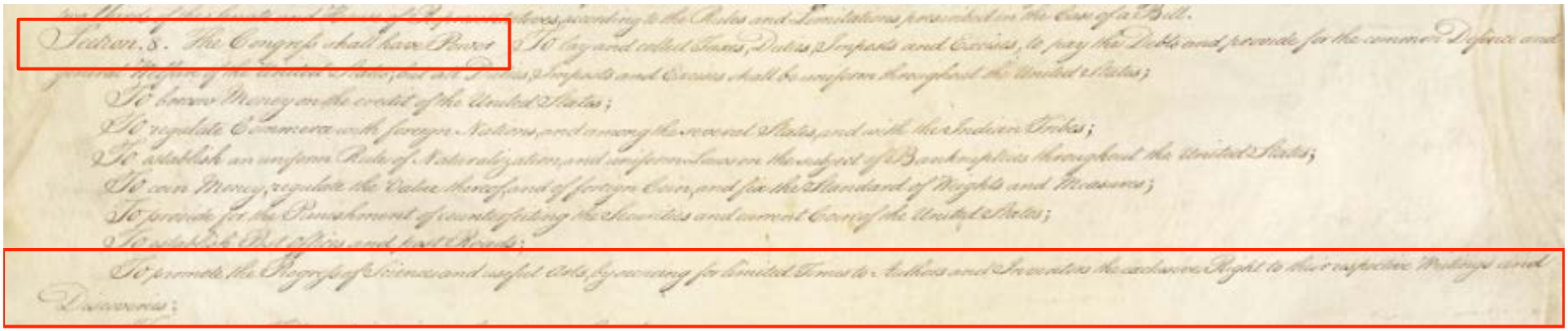

We The People of the United States, in order to form a more perfect Union, establish Justice, insure domestic Tranquility, provide for the common defence, promote the general Welfare, and secure the Blessings of Liberty to ourselves and our Posterity, do ordain and establish this Constitution for the United States of America.

Article. I.

Section. 1. All legislative Powers herein granted shall be vested in a Congress of the United States, which shall consist of a Senate and House of Representatives.

The Congress shall have Power…
… To promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries….

ARTICLE I, SECTION 8, CLAUSE 8


Section. 8. The Congress shall have Power To lay and collect Taxes, Duties, Imposts and Excises, to pay the Debts and provide for the common Defence and general Welfare of the United States; but all Duties, Imposts and Excises shall be uniform throughout the United States;
To borrow Money on the credit of the United States;
To regulate Commerce with foreign Nations, and among the several States, and with the Indian Tribes;
To establish an uniform Rule of Naturalization, and uniform Laws on the subject of Bankruptcies throughout the United States;
To coin Money, regulate the Value thereof, and of foreign Coin, and fix the Standard of Weights and Measures;
To provide for the Punishment of counterfeiting the Securities and current Coin of the United States;
To establish Post Offices and post Roads;
To promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries;

The Patent Families in the Dispute:

(12) **United States Patent**
Barany et al.

(10) **Patent No.: US 6,797,470 B2**
(45) **Date of Patent: Sep. 28, 2004**

Filed
May 29, 1996

(54) **DETECTION OF NUCLEIC ACID SEQUENCE DIFFERENCES USING COUPLED LIGASE DETECTION AND POLYMERASE CHAIN REACTIONS**

(75) Inventors: **Francis Barany**, New York, NY (US); **Matthew Lubin**, Rye Brook, NY (US); **George Barany**, Falcon Heights, MN (US); **Robert P. Hammer**, Baton Rouge, LA (US)

5,035,996 A	7/1991	Hartley
5,143,854 A	9/1992	Pirrung et al.

(List continued on next page.)

FOREIGN PATENT DOCUMENTS

EP	WO 92/10588	6/1992
EP	WO 92/16655	10/1992
EP	WO 93/17126	9/1993
EP	WO 93/20236	10/1993
EP	0 601 714 A1	6/1994
EP	WO 96/06190	2/1996

(12) **United States Patent**
Barany et al.

(10) **Patent No.: US 7,083,917 B2**
(45) **Date of Patent: *Aug. 1, 2006**

Filed
Feb 9, 1996

(54) **DETECTION OF NUCLEIC ACID SEQUENCE DIFFERENCES USING THE LIGASE DETECTION REACTION WITH ADDRESSABLE ARRAYS**

(75) Inventors: **Francis Barany**, New York, NY (US); **George Barany**, Falcon Heights, MN (US); **Robert P. Hammer**, Baton Rouge, LA (US); **Maria Kempe**, Minneapolis, MN (US); **Herman Blok**, Wemeldinge (NL); **Monib Zirvi**, New York, NY (US)

5,143,854 A	9/1992	Pirrung et al.
5,202,231 A	4/1993	Drmanac et al.
5,258,506 A	11/1993	Urdea et al.
5,278,298 A	1/1994	Chakraborty et al.
5,288,468 A	2/1994	Church et al.
5,290,925 A	3/1994	Fino
5,314,809 A	5/1994	Erlich et al.
5,324,633 A	6/1994	Fodor et al.
5,352,582 A	10/1994	Lichtenwalter et al.
5,371,241 A	12/1994	Brush et al.
5,391,480 A	2/1995	Davis et al.
5,405,783 A	4/1995	Pirrung et al.
5,407,798 A	4/1995	Martinelli et al.
5,412,087 A	5/1995	McGall et al.

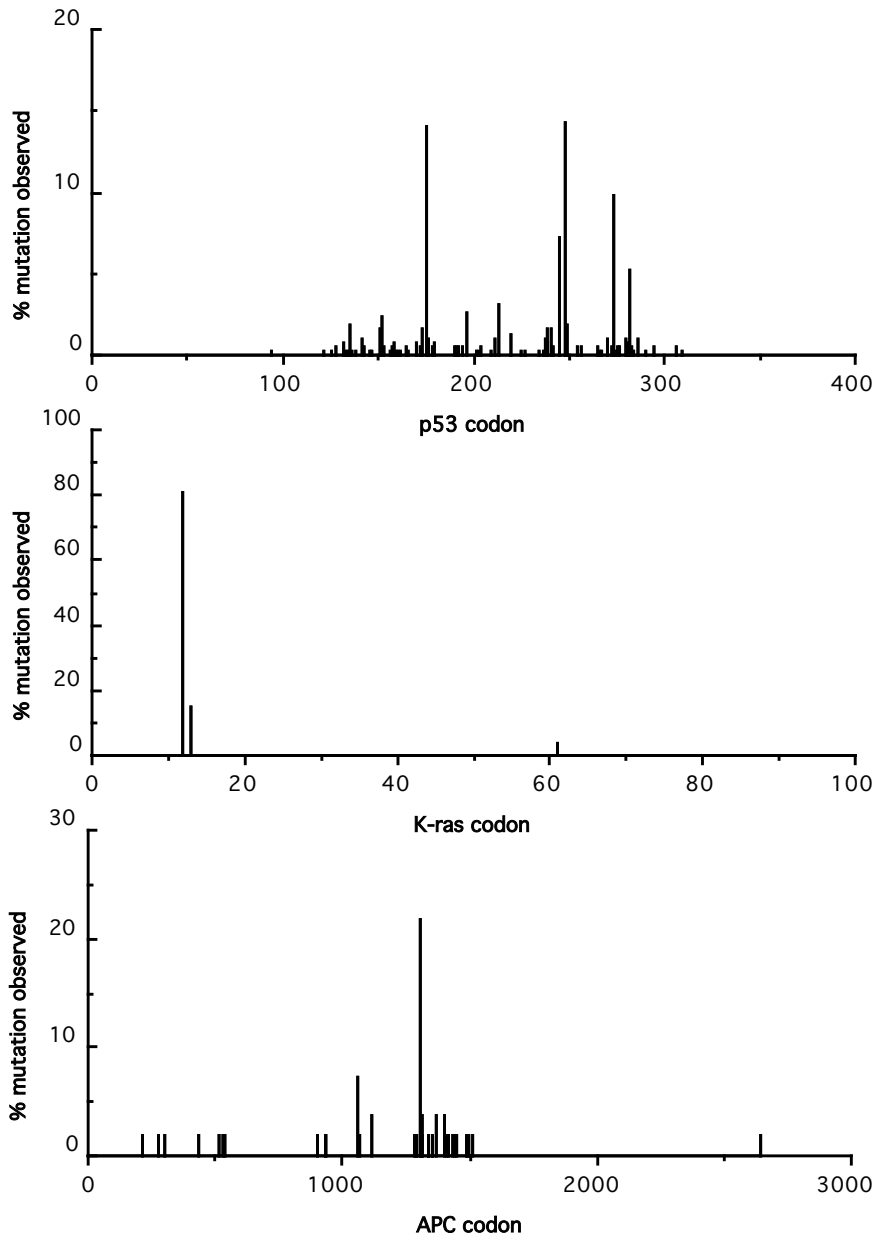
Mutations observed in Colon Tumors

Challenges:

1. **Stromal contamination: Mutation may be present in only 15%-25% of DNA.**

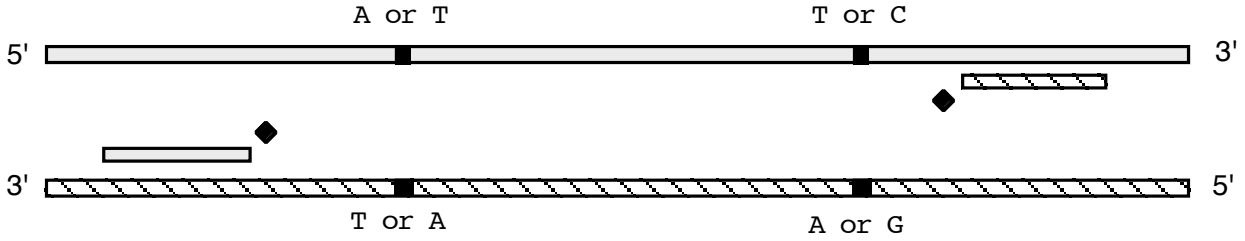
2. **Multiple, and closely spaced mutations in multiple genes.**

3. **For early detection, need to find one mutant in 100 (or higher) wild-type.**

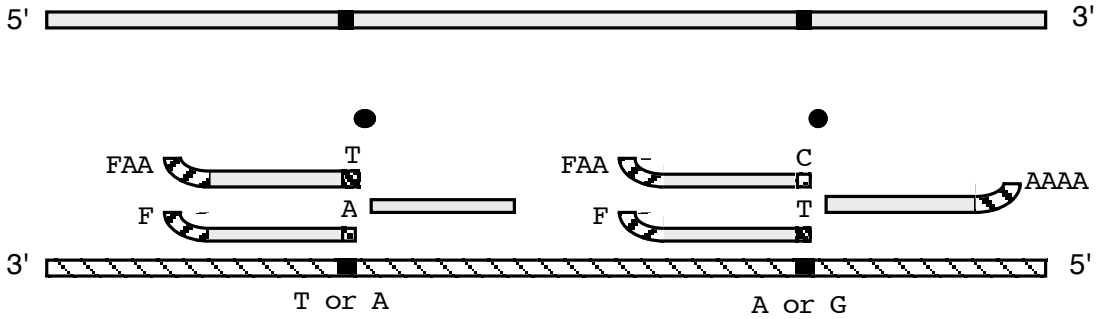


PCR/ LDR

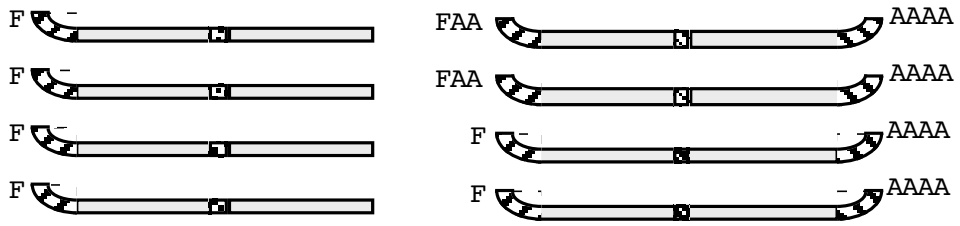
1. PCR amplify region(s) containing mutations using primers, dNTPs and *Taq* polymerase. ◆



2. Add LDR primers and thermostable ligase. ● Denature DNA, 94°C. Anneal and ligate at 65°C. Allele specific oligonucleotides ligate to common oligonucleotides only when there is perfect complementarity at the junction.



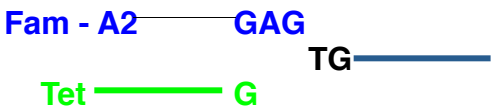
3. Repeat cycle 2 to 10 times. Separate fluorescent products on DNA sequencer and quantify each allele.



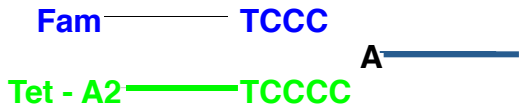
Homozygous: T allele only. Heterozygous: A and G alleles.

BRCA 1 and 2 Germline Mutations

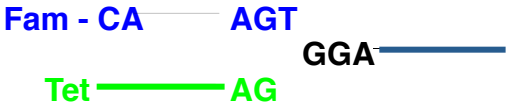
BRCA1 exon 2
185delAG

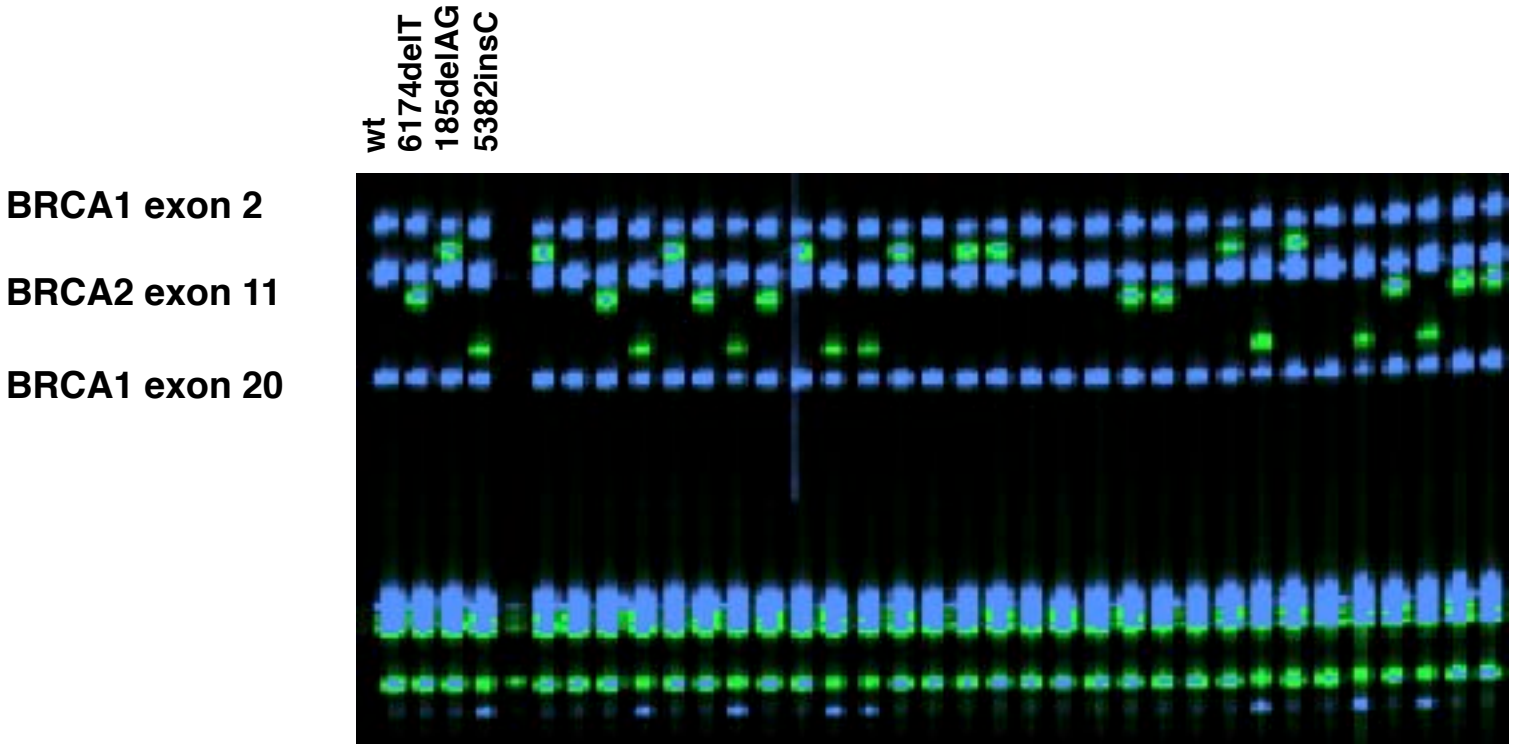


BRCA1 exon 20
5382insC

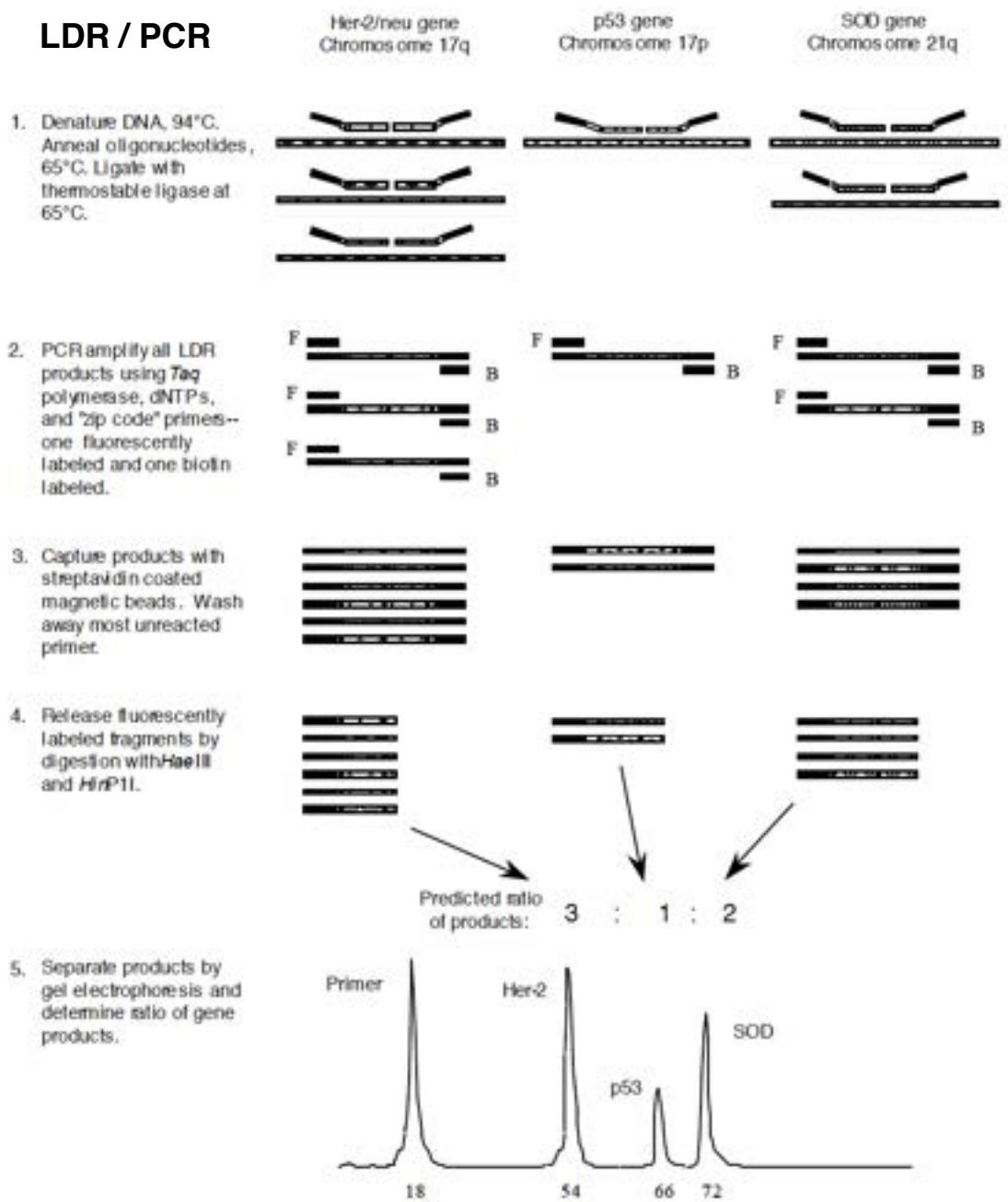


BRCA2 exon 11
6174delT

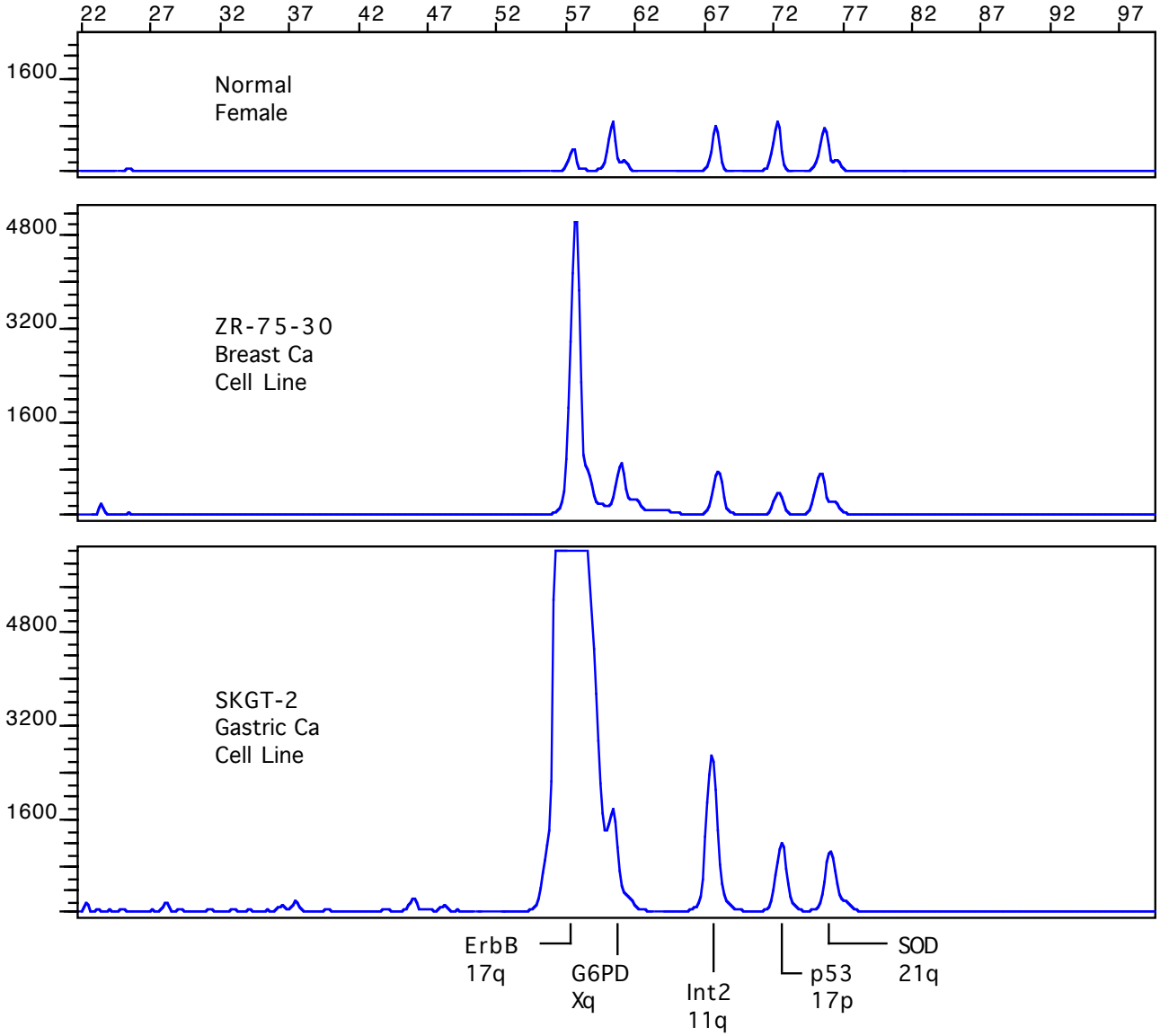




LDR / PCR

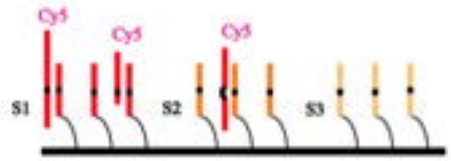

Her-2/neu gene
Chromosome 17q
p53 gene
Chromosome 17p
SOD gene
Chromosome 21q
1. Denature DNA, 94°C. Anneal oligonucleotides, 65°C. Ligate with thermostable ligase at 65°C.
2. PCR amplify all LDR products using Taq polymerase, dNTPs, and "zip code" primers--one fluorescently labeled and one biotin labeled.
F
B
3. Capture products with streptavidin coated magnetic beads. Wash away most unreacted primer.
4. Release fluorescently labeled fragments by digestion with Hae III and HinP1I.
Predicted ratio of products: 3 : 1 : 2
5. Separate products by gel electrophoresis and determine ratio of gene products.
Primer
Her-2
p53
SOD
18
54
66
72

Amplification of ErbB (Her2 gene)



Comparison of Arrays for Identifying Mutations

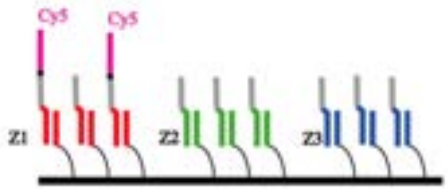
<u>Hybridization Arrays</u>:



• Discrimination based on match vs. mismatch hybridization; probes are very similar in sequence.

• Tm (melting temperature) of probes depend on target; considerable variation.

<u>Universal Arrays</u>:



• Discrimination based on match vs. mismatch ligation.

• Capture probes designed to have distinct sequences with no cross-hybridization.

Identifying Mutations by Hybridization: 2

Target: 5'-CATTAAAGAAAATATCATCTTTGGTGTTTCCTATGATGA

Probes:

3'-TTTATAGTAGAAACC (SEQ. ID NO:9G)
3'-TTTATAATAGAAACC (SEQ. ID NO:9A)
3'-TTTATATTAGAAACC (SEQ. ID NO:9T)
3'-TTTATACTAGAAACC (SEQ. ID NO:9C)

3'-TTATAGTAGAAACCA (SEQ. ID NO:10T)
3'-TTATAGCAGAAACCA (SEQ. ID NO:10C)
3'-TTATAGGAGAAACCA (SEQ. ID NO:10G)
3'-TTATAGAAGAAACCA (SEQ. ID NO:10A)

3'-TATAGTAGAAACCAC (SEQ. ID NO:11A)
3'-TATAGTTGAAACCAC (SEQ. ID NO:11T)
3'-TATAGTCGAAACCAC (SEQ. ID NO:11C)
3'-TATAGTGGAAACCAC (SEQ. ID NO:11G)

Identifying Mutations by Hybridization: 3

Target: 5'-CATTAAAGAAAATATCATCTTTGGTGTTTCCTATGATGA

Probes:

3'-TTTATAGTAGAAACC (SEQ. ID NO:9G)

3'-TTTATAATAGAAACC (SEQ. ID NO:9A)

Probes: 93% Identical

3'-TTTATATTAGAAACC (SEQ. ID NO:9T)

3'-TTTATACTAGAAACC (SEQ. ID NO:9C)

Target: 5'-CATTAAAGAAAATATCATCTTTGGTGTTTCCTATGATGA

3'-TTATAGTAGAAACCA (SEQ. ID NO:10T)

87% Identical

3'-TTATAGCAGAAACCA (SEQ. ID NO:10C)

Target: 5'-CATTAAAGAAAATATC^A^TCTTTGGTGTTTCCTATGATGA

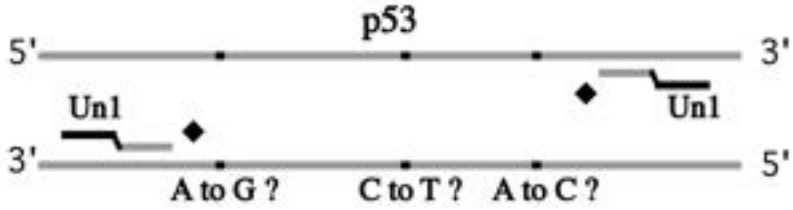
3'-TTATAGGAGAAACCA (SEQ. ID NO:10G)

3'-TTATAGAAGAAACCA (SEQ. ID NO:10A)

93% Identical

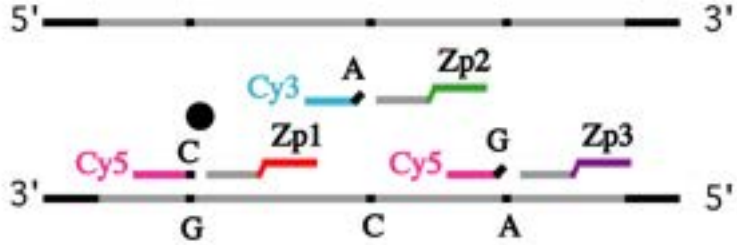
PCR / PCR / LDR / Universal Array

1. PCR amplify all p53 exons using gene-specific/universal primers and Taq polymerase. ◆

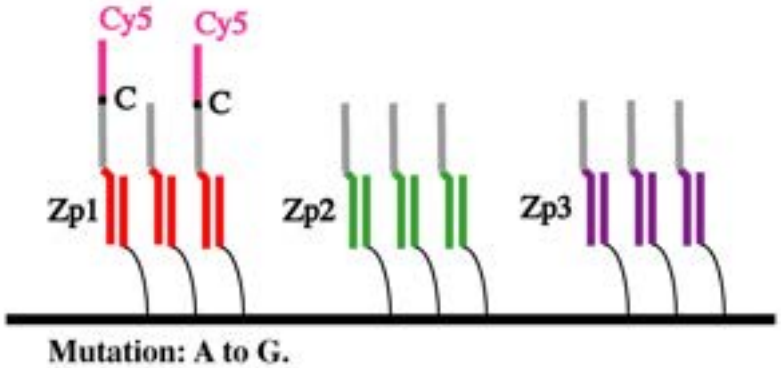


2. PCR amplify all primary products using universal primers and Taq polymerase. ◆

3. Perform LDR using mutation-specific LDR primers, common primers containing complementary zip code sequences, and thermostable ligase. ●



4. Capture fluorescent products on addressable array and score for presence of mutation.



Favis R, Huang J, Gerry NP, Culliford A, Paty P, Soussi T, Barany F. Hum Mutat. 2004 Jul;24(1):63-75.

Identifying Mutations by Zipcode Arrays: 1

Probes: Zip 12 (2-4-4-6-1-1)=24 mer

Probes:

Target: 3'-TAGC CCAT CCAT TGGA ACGC ACGC - LDR PRODUCT 1
5'-ATCG GGTA GGTA ACCT TGCG TGCG-3' SEQ ID NO: 7

50% Identical

Zip 14 (4-4-6-6-3-1)=24 mer

Target: 3'-CCAT CCAT TGGA TGGA GTCG ACGC - LDR PRODUCT 2
5'-GGTA GGTA ACCT ACCT CAGC TGCG-3' SEQ ID NO: 8

Identifying Mutations by Zipcode Arrays: 2

Probes: Zip 12 (2-4-4-6-1-1)=24 mer

Target: 3'-TAGC CCAT CCAT TGGA ACGC ACGC - LDR PRODUCT 1
5'-ATCG GGTA GGTA ACCT TGCG TGCG-3' SEQ ID NO: 7

24/24 match
Yes hybridization

Probes:
25% or more
Different

Zip 14 (4-4-6-6-3-1)=24 mer

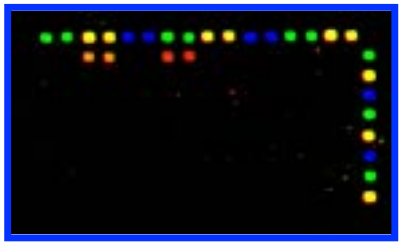
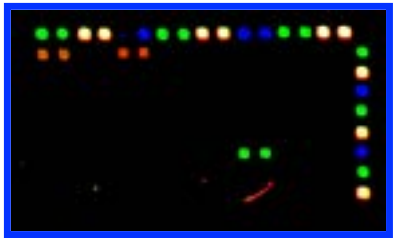
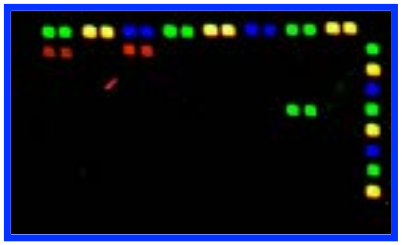
Target: 3'-TAGC CCAT CCAT TGGA ACGC ACGC - LDR PRODUCT 1
5'-GGTA GGTA ACCT ACCT CAGC TGCG-3' SEQ ID NO: 8

12/24 match
No hybridization

Target: 3'-TAGC CCAT CCAT TGGA AC$_G$C ACGC - LDR PRODUCT 1
5'-GGTA GGTA ACCT ACCT CAGC TGCG-3' SEQ ID NO: 8

13/24 match
No hybridization

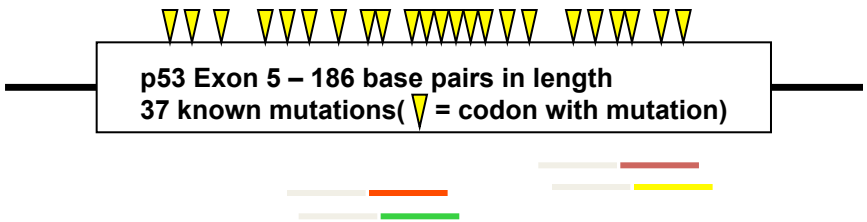
Detection of Mutations in Colon Tumor DNA using the p53 Chip

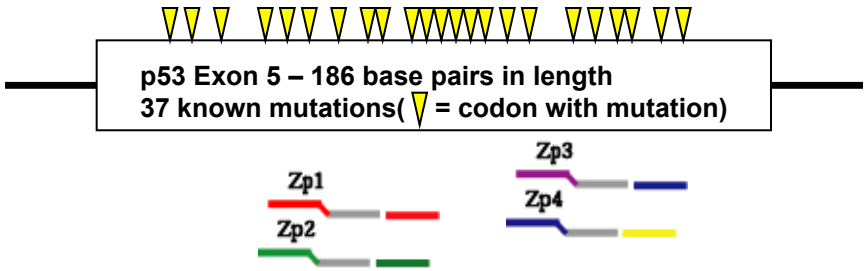
	Upper Strand	Lower Strand	Mutation
Sample 1			**R273 C-T** **Lower strand** **Zip 46**
Sample 2			**Y220 A-G** **Lower strand** **Zip 31**
Sample 3			**R175 G2-A** **Upper strand** **Zip 21**

Cy 3 **Cy 5** **FAM**

Favis R, Huang J, Gerry NP, Culliford A, Paty P, Soussi T, Barany F. Hum Mutat. 2004 Jul;24(1):63-75.

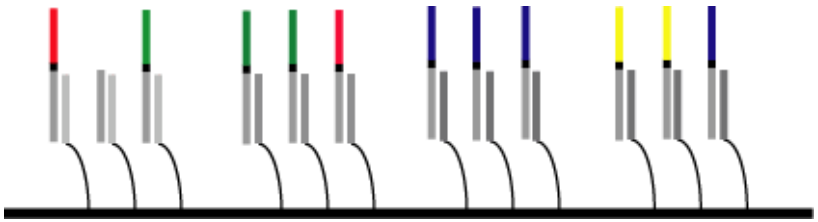
Comparison of Array Hybridization Results When Mutations are Closely Spaced

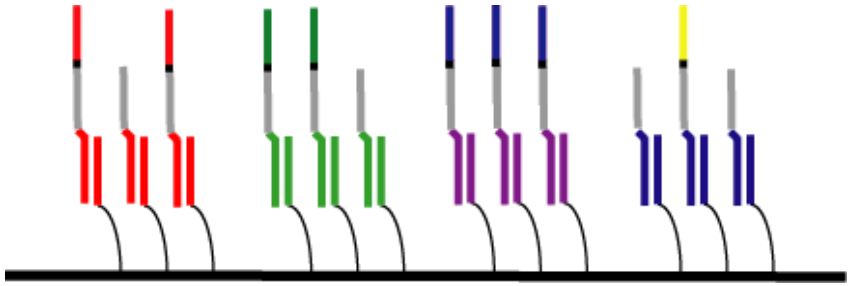




Hybridization capture probes are complementary to unlabeled primer

Hybridization capture Probes are Zipcodes



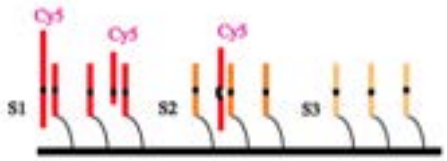


Results: Incorrect Signals due to Cross-Hybridization

Results: Only Correct Signal at Each Zipcode

Advantage of Universal Arrays over Hybridization Arrays

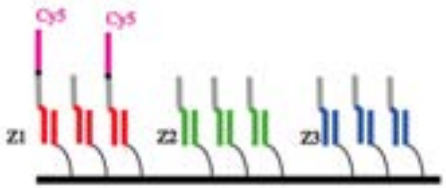
Hybridization Arrays:



- Discrimination based on match vs. mismatch hybridization; probes are very similar in sequence.

- Cross-hybridization between perfect match and mismatch probes leads to false-positives and false-negatives.

Universal Arrays:



- Capture-specific probe sequences designed to differ by 25% or more to minimize cross-hybridization.

- Composite probes or products containing a target-specific portion and a capture-specific portion allow for accurate target identification.

Subject Privileged and Confidential: Detailed Case Summary and Strategic Alignment: Cornell and Akin Gump Only; Parts 4 & 5

From Francis Barany <barany@med.cornell.edu>

To: Valerie Cross <vlc1@cornell.edu>, Pearson, Matthew <mpearson@AKINGUMP.com>, Weil, Jason <jweil@akingump.com>

Cc: Dianne Elderkin <delderkin@akingump.com>, Gary Koretzky <gak2008@med.cornell.edu>, Carl F. Nathan <cnathan@med.cornell.edu>, Brian Kelly <bjk44@cornell.edu>, Monib Zirvi <matzirvi@yahoo.com>, Francis Barany <barany@med.cornell.edu>

Date Dec 19, 2016 at 3:07 PM

Francis

[redacted]

barany@med.cornell.edu

[redacted]

Cornell_Illumina_Case_Confidential_Su…

Cornell_Illumina_Case_Confidential_Su…

Subject Privileged and Confidential: Detailed Case Summary and Strategic Alignment: Cornell and Akin Gump Only; Parts 6 & 7

From Francis Barany <barany@med.cornell.edu>

To: Valerie Cross <vlc1@cornell.edu>, Pearson, Matthew <mpearson@AKINGUMP.com>, Weil, Jason <jweil@akingump.com>

Cc: Dianne Elderkin <delderkin@akingump.com>, Gary Koretzky <gak2008@med.cornell.edu>, Carl F. Nathan <cnathan@med.cornell.edu>, Brian Kelly <bjk44@cornell.edu>, Monib Zirvi <matzirvi@yahoo.com>, Francis Barany <barany@med.cornell.edu>

Date Dec 19, 2016 at 3:09 PM

Francis

[redacted]

barany@med.cornell.edu

[redacted]

Cornell_Illumina_Case_Confidential_Su…

Cornell_Illumina_Case_Confidential_Su…

Subject Privileged and Confidential: Detailed Case Summary and Strategic Alignment: Cornell and Akin Gump Only; Parts 8 & 9

From Francis Barany <barany@med.cornell.edu>

To: Valerie Cross <vlc1@cornell.edu>, Pearson, Matthew <mpearson@AKINGUMP.com>, Weil, Jason <jweil@akingump.com>

Cc: Dianne Elderkin <delderkin@akingump.com>, Gary Koretzky <gak2008@med.cornell.edu>, Carl F. Nathan <cnathan@med.cornell.edu>, Brian Kelly <bjk44@cornell.edu>, Monib Zirvi <matzirvi@yahoo.com>, Francis Barany <barany@med.cornell.edu>

Date Dec 19, 2016 at 3:09 PM

Last email, kindly confirm receipt.

9 total attachments, chapters of 184 page powerpoint.

Thanks!

Francis

[redacted]

barany@med.cornell.edu

[redacted]

Cornell_Illumina_Case_Confidential_Su…

Cornell_Illumina_Case_Confidential_Su…

Subject RE: Privileged and Confidential: Detailed Case Summary and Strategic Alignment: Cornell and Akin Gump Only; Parts 8 & 9

From Weil, Jason <jweil@akingump.com>

To: Francis Barany <barany@med.cornell.edu>, Valerie Cross <vlc1@cornell.edu>, Pearson, Matthew <mpearson@AKINGUMP.com>

Cc: Elderkin, Dianne <delderkin@AKINGUMP.com>, Gary Koretzky <gak2008@med.cornell.edu>, Carl F. Nathan <cnathan@med.cornell.edu>, Brian Kelly <bjk44@cornell.edu>, Monib Zirvi <matzirvi@yahoo.com>

Date Dec 19, 2016 at 3:25 PM

Hi Francis,

We received them all.

Thanks,
Jason

From: Francis Barany [mailto:barany@med.cornell.edu]
Sent: Monday, December 19, 2016 12:09 PM
To: Valerie Cross; Pearson, Matthew; Weil, Jason
Cc: Elderkin, Dianne; Gary Koretzky; Carl F. Nathan; Brian Kelly; Monib Zirvi; Francis Barany
Subject: Privileged and Confidential: Detailed Case Summary and Strategic Alignment: Cornell and Akin Gump Only; Parts 8 & 9
Importance: High

Last email, kindly confirm receipt.

9 total attachments, chapters of 184 page powerpoint.

Thanks!

Francis

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

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Subject Re: Privileged and Confidential: Detailed Case Summary and Strategic Alignment: Cornell and Akin Gump Only; Parts 8 & 9

From Francis Barany <barany@med.cornell.edu>

To: Weil, Jason <jweil@akingump.com>

Cc: Valerie Cross <vlc1@cornell.edu>, Pearson, Matthew <mpearson@AKINGUMP.com>, Elderkin, Dianne <delderkin@AKINGUMP.com>, Brian Kelly <bjk44@cornell.edu>, Monib Zirvi <matzirvi@yahoo.com>

Date Dec 19, 2016 at 3:32 PM

Dear Jason,

Thanks.

You may have seen the most recent class action lawsuit against Illumina…to wish I politely say: “Get in line, please."

Also, would you please let me know ASAP if we are confirmed for my deposition on January 18th?

Most appreciated,

Francis

[redacted]
barany@med.cornell.edu

[redacted]

Class Action Lawsuit Against Illumina Alleges Firm and Two Officials Misled Investors

Dec 19, 2016 | a GenomeWeb staff reporter

NEW YORK (GenomeWeb) – Two shareholders have

filed a class action lawsuit against Illumina and two of its top officials, claiming that the defendants made materially false and misleading statements regarding the firm's business, operations, and prospects between the announcement of Illumina's second quarter and preliminary third quarter financial results that led to an inflated share price.

Plaintiffs Yi Fan Chen and Frontline Global Trading, of which Chen is president, filed the suit last Friday in the US District Court for the Southern District of California on behalf of a class that consists of persons and entities that bought Illumina securities between July 26 and October 10 of this year. The defendants are Illumina; President and CEO Francis deSouza; and Executive Vice President, Chief Administrative Officer, and CFO Marc Stapley.

On July 26, Illumina announced its second quarter earnings, which included revenue guidance of between $625 million and $630 million for the third quarter. On Oct. 10, the company released preliminary revenues for the third quarter that fell $18 million to $23 million short of that guidance, leading to a drop of Illumina's share price by about 25 percent at the end of that day.

Illumina said at the time that the revenue shortfall was driven by "a larger than anticipated year-over-year decline in high-throughput sequencing instruments."

According to the complaint, the defendants allegedly failed to disclose prior to October 10 that Illumina was experiencing a large decline in high-throughput sequencing instrument sales that was impacting its revenue, that they lacked visibility into trends that could impact its financial results substantially, that they provided unreliable and overstated revenue guidance, and that they made false and misleading positive statements about Illumina's business, operations, and prospects.

As a result, the company's shares traded "at artificially inflated prices" during the class period, according to the plaintiffs, and because of the "precipitous decline" in the market value of Ilumina's shares after the Oct. 10 announcement, the plaintiffs and other class members

"suffered significant losses and damages."

The plaintiffs asked the court to award them and the other class members compensatory damages of a yet-to-be determined amount, as well as costs and expenses.

Illumina's shares dropped less than 1 percent to $130.16 in afternoon trading on the Nasdaq.

The company declined to comment on the lawsuit.

On Dec 19, 2016, at 3:25 PM, Weil, Jason <jweil@akingump.com> wrote:

Hi Francis,

We received them all.

Thanks,
Jason

From: Francis Barany [mailto:barany@med.cornell.edu]
Sent: Monday, December 19, 2016 12:09 PM
To: Valerie Cross; Pearson, Matthew; Weil, Jason
Cc: Elderkin, Dianne; Gary Koretzky; Carl F. Nathan; Brian Kelly; Monib Zirvi; Francis Barany
Subject: Privileged and Confidential: Detailed Case Summary and Strategic Alignment: Cornell and Akin Gump Only; Parts 8 & 9
Importance: High

Last email, kindly confirm receipt.

9 total attachments, chapters of 184 page powerpoint.

Thanks!

Francis

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

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Subject Re: Privileged and Confidential: Detailed Case Summary and Strategic Alignment: Cornell and Akin Gump Only; Part 10

From Francis Barany <barany@med.cornell.edu>

To: Valerie Cross <vlc1@cornell.edu>, Pearson, Matthew <mpearson@AKINGUMP.com>, Weil, Jason <jweil@akingump.com>

Cc: Dianne Elderkin <delderkin@akingump.com>, Brian Kelly <bjk44@cornell.edu>, Monib Zirvi <matzirvi@yahoo.com>, Francis Barany <barany@med.cornell.edu>

Date Jan 6, 2017 at 6:48 PM

Dear Valerie, Matthew, and Jason,

Over the last few weeks, we have scoured numerous publicly available documents directly related to our case. After this work, a clear picture of supporting evidence has emerged to help elucidate how Illumina willfully and deceitfully attempted to defraud Cornell's IP.

Our research has led to a number of important questions below that need to be resolved.

Kindly find enclosed some additional sections of our master Powerpoint – we are not resending you older files (other than a review of summaries) you already have those from our emails to you on December 19th.

We are also sending supporting documentation of a series of patent applications by Fan, Fan & Chee, and Fan & Fu.

Further, because Illumina recently revamped their product lines on their web-site, we reanalyzed their

product line, using stringent criteria for inclusion in the infringement category. Even we were shocked to see that 94% of their products infringed on

to see that 94% of their products infringed on Cornell's IP.* We will provide those documents in followup emails.

We are sending these files tonight to provide you some time to review prior to our Tuesday Phone meeting.

Kindly confirm receipt.

Best,

Francis & Monib

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

*(excluding rRNA removal kits).

---

1. Does Akin-Gump have access to the Affymetrix files – now that the company is part of ThermoFisher? Would you be able to find minutes of meetings where Mark Chee, Kevin Gunderson, and/or J.B. Fan were present during discussion between Mike Hunkapiller of ABI with Steve Fodor of Affymetrix concerning zip code arrays, which Affymetrix renamed "Tag Arrays"? Would you be able to find such files from the ABI side?

2. Did the discovery reveal documents from Illumina where they refer to zip code sequences and Tag sequences in the same document? Further, are there additional documents where, "OLA" or "GoldenGate" are mentioned with "Illumacodes", "Tag sequences", "Adapter sequences", "Decoder Binding Ligands", and "Identifier Binding Ligands", or "Zipcode sequences".

3. How much can we bring in that some of the "co-inventors" are serial copycats, from Affymetrix, to Illumina, to Ariosa?

In fact Illumina is now suing Ariosa for IP:
- which Oliphant and Stuelpnagel took from Illumina,
- which Chee, Gunderson and Fan while at Illumina took from Affymetrix and Barany,
- which Fodor, Chee, Gunderson and Fan while at Affymetrix also took from Barany?

4. We developed the “addressable array”, while Illumina only had randomly “assembled array”. It wasn’t until after Illumina got access to our zip code chemistry, that they could make their assembled arrays into addressable or universal arrays. If the arrays are not addressable, they will not work. Would you be able to determine when Illumina switched from the term “assembled array” to the term “address” and “addressable array” in their patents and internal documents?

5. In the trial, if it is known, can it be revealed if the 16 zip codes Illumina initially used were the original 16 Barany zip codes from our list? How will the Norman Gerry Patent or Paper with these sequences in them be introduced or presented at trial?

6. Illumina says 1536 – 16 = 1520 zipcodes worked in their US7226734 patent, same number as Gunderson et al. 2004 paper. Matthew, do you know if any of the 16 zip codes removed were the Barany 16 zip codes? Did they really fail to have 16 zip codes working, or did they deliberately mislead as to hide the true nature of what they did?

7. During the Ariosa-Illumina IPR, Stuelpnagel’s deposition from the Zebala/Syntrix suit was presented. Is there any way to introduce the Ariosa – Illumina IPR and use any of the testimony at trial? (e.g. claim construction on “solid support”). If Zebala/Syntrix is even accidentally or inadvertently introduced by witnesses at our trial, will it be considered prejudicial and possible grounds for appeal or will the judge ask the jury to disregard it?

8. Walt and Chee played critical roles at Illumina. Chee attempted to file or filed numerous patents and Walt played an important supervisory and scientific role. Walt was mentioned by name in

scientific role. Walt was mentioned by name in a provisional patent application which included reference to our original zip code chemistry and Universal zip code arrays. Can the fact that Walt and Chee did not appear in their defense be presented? Wouldn't it look like a tacit/implied admission of guilt on the part of the defendant?

9. Will the Joint Development Agreement and the First Amendment to that agreement be presented in the trial? Can Illumina use the third document with covenant not to sue at this trial? Is there any portion of the three documents that Illumina can use in their defense strategy? What are our counter-arguments?

10. What were the lessons learned from the Columbia-Illumina trial? How do we properly make sure that Edward Reines, or all of Weil, Gotshal & Manges LLP is disqualified from representing Illumina in this case due to a personal conflict of interest?

11. Can you find the original submission of the enclosed patent application: CA2399733C - Nucleic acid detection methods using universal priming submitted by Fan & Chee on Feb. 7, 2000 with the full-length abstract?

View less

PastedGraphic-1.pdf

CA2399733C - Nucleic acid detection m…

Subject Re: Privileged and Confidential: Detailed Case Summary and Strategic Alignment: Cornell and Akin Gump Only; Part 11

From Francis Barany <barany@med.cornell.edu>

To: Valerie Cross <vlc1@cornell.edu>, Pearson, Matthew <mpearson@AKINGUMP.com>, Weil, Jason <jweil@akingump.com>

Cc: Dianne Elderkin <delderkin@akingump.com>, Brian Kelly <bjk44@cornell.edu>, Monib Zirvi <matzirvi@yahoo.com>, Francis Barany <barany@med.cornell.edu>

Date Jan 6, 2017 at 6:49 PM

Confidential Powerpoint parts of overall case (previous parts were sent on 12/19/2016)

Francis

[redacted]
barany@med.cornell.edu

[redacted]

Cornell_Illumina_Case_Confidential_Su…

Cornell_Illumina_Case_Confidential_Su…

Cornell_Illumina_Case_Confidential_Su…

Subject Re: Privileged and Confidential: Detailed Case Summary and Strategic Alignment: Cornell and Akin Gump Only; Part 12

From Francis Barany <barany@med.cornell.edu>

To: Valerie Cross <vlc1@cornell.edu>, Pearson, Matthew <mpearson@AKINGUMP.com>, Weil, Jason <jweil@akingump.com>

Cc: Dianne Elderkin <delderkin@akingump.com>, Brian Kelly <bjk44@cornell.edu>, Monib Zirvi <matzirvi@yahoo.com>, Francis Barany <barany@med.cornell.edu>

Date Jan 6, 2017 at 6:52 PM

Francis

[redacted]

barany@med.cornell.edu

[redacted]

Illumina Chart Figures 2014-2016_v07_…

Subject Re: Privileged and Confidential: Detailed Case Summary and Strategic Alignment: Cornell and Akin Gump Only; Part 13

From Francis Barany <barany@med.cornell.edu>

To: Valerie Cross <vlc1@cornell.edu>, Pearson, Matthew <mpearson@AKINGUMP.com>, Weil, Jason <jweil@akingump.com>

Cc: Dianne Elderkin <delderkin@akingump.com>, Brian Kelly <bjk44@cornell.edu>, Monib Zirvi <matzirvi@yahoo.com>, Francis Barany <barany@med.cornell.edu>

Date Jan 6, 2017 at 6:53 PM

Francis

[redacted]

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[redacted]

Illumina Chart Figures 2014-2016_v07_…

Subject Re: Privileged and Confidential: Detailed Case Summary and Strategic Alignment: Cornell and Akin Gump Only; Part 14

From Francis Barany <barany@med.cornell.edu>

To: Valerie Cross <vlc1@cornell.edu>, Pearson, Matthew <mpearson@AKINGUMP.com>, Weil, Jason <jweil@akingump.com>

Cc: Dianne Elderkin <delderkin@akingump.com>, Brian Kelly <bjk44@cornell.edu>, Monib Zirvi <matzirvi@yahoo.com>, Francis Barany <barany@med.cornell.edu>

Date Jan 6, 2017 at 6:54 PM

Francis

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[redacted]

60180810_Fan_Fu_02_07_2000.pdf

60234731_Fan_Fu_09_22_2000.pdf

Subject Re: Privileged and Confidential: Detailed Case Summary and Strategic Alignment: Cornell and Akin Gump Only; Part 15

From Francis Barany <barany@med.cornell.edu>

To: Valerie Cross <vlc1@cornell.edu>, Pearson, Matthew <mpearson@AKINGUMP.com>, Weil, Jason <jweil@akingump.com>

Cc: Dianne Elderkin <delderkin@akingump.com>, Brian Kelly <bjk44@cornell.edu>, Monib Zirvi <matzirvi@yahoo.com>, Francis Barany <barany@med.cornell.edu>

Date Jan 6, 2017 at 6:55 PM

Francis

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[redacted]

60311194_Fan_Fu_08_09_2001.pdf

Subject Re: Privileged and Confidential: Detailed Case Summary and Strategic Alignment: Cornell and Akin Gump Only; Part 16

From Francis Barany <barany@med.cornell.edu>

To: Valerie Cross <vlc1@cornell.edu>, Pearson, Matthew <mpearson@AKINGUMP.com>, Weil, Jason <jweil@akingump.com>

Cc: Dianne Elderkin <delderkin@akingump.com>, Brian Kelly <bjk44@cornell.edu>, Monib Zirvi <matzirvi@yahoo.com>, Francis Barany <barany@med.cornell.edu>

Date Jan 6, 2017 at 6:55 PM

Francis

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barany@med.cornell.edu

[redacted]

09779202_Fan_Fu_Fig_1-11_02_07_2…

09779376_Fan_Fu_Fig_1-10_02_07_2…

Subject Re: Privileged and Confidential: Detailed Case Summary and Strategic Alignment: Cornell and Akin Gump Only; Part 17

From Francis Barany <barany@med.cornell.edu>

To: Valerie Cross <vlc1@cornell.edu>, Pearson, Matthew <mpearson@AKINGUMP.com>, Weil, Jason <jweil@akingump.com>

Cc: Dianne Elderkin <delderkin@akingump.com>, Brian Kelly <bjk44@cornell.edu>, Monib Zirvi <matzirvi@yahoo.com>, Francis Barany <barany@med.cornell.edu>

Date Jan 6, 2017 at 6:56 PM

Francis

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[redacted]

US6890741_Fan_St_Chee_Fig_1-12_0…

US6913884_Stuelpnagel_Chee_08_16…

Subject Re: Privileged and Confidential: Detailed Case Summary and Strategic Alignment: Cornell and Akin Gump Only; Part 18

From Francis Barany <barany@med.cornell.edu>

To: Valerie Cross <vlc1@cornell.edu>, Pearson, Matthew <mpearson@AKINGUMP.com>, Weil, Jason <jweil@akingump.com>

Cc: Dianne Elderkin <delderkin@akingump.com>, Brian Kelly <bjk44@cornell.edu>, Monib Zirvi <matzirvi@yahoo.com>, Francis Barany <barany@med.cornell.edu>

Date Jan 6, 2017 at 6:56 PM

Francis

[redacted]

barany@med.cornell.edu

[redacted]

US20020132241_Fan_St_Chee_Fig_1-…

US20030104434_Fan_Fu_Fig_1-18_08…

Subject Re: Privileged and Confidential: Detailed Case Summary and Strategic Alignment: Cornell and Akin Gump Only; Part 19

From Francis Barany <barany@med.cornell.edu>

To: Valerie Cross <vlc1@cornell.edu>, Pearson, Matthew <mpearson@AKINGUMP.com>, Weil, Jason <jweil@akingump.com>

Cc: Dianne Elderkin <delderkin@akingump.com>, Brian Kelly <bjk44@cornell.edu>, Monib Zirvi <matzirvi@yahoo.com>, Francis Barany <barany@med.cornell.edu>

Date Jan 6, 2017 at 6:58 PM

Francis

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barany@med.cornell.edu

[redacted]

WO2001057268A2_Fan_Fu_Fig_1-11_…

WO2001057269-PAMPH-65d_Fan_Fig…

Subject Re: Privileged and Confidential: Detailed Case Summary and Strategic Alignment: Cornell and Akin Gump Only; Part 20

From Francis Barany <barany@med.cornell.edu>

To: Valerie Cross <vlc1@cornell.edu>, Pearson, Matthew <mpearson@AKINGUMP.com>, Weil, Jason <jweil@akingump.com>

Cc: Dianne Elderkin <delderkin@akingump.com>, Brian Kelly <bjk44@cornell.edu>, Monib Zirvi <matzirvi@yahoo.com>, Francis Barany <barany@med.cornell.edu>

Date Jan 7, 2017 at 2:10 PM

Dear Valerie, Matthew, and Jason,

As per page 20 of the enclosed “Petitioners Demonstrative Exhibits” (prepared by Ariosa) it finds within 60/180810 "the ‘810 provisional application” of Fan & Fu states that" Illumina had 128 unique addresses that hybridize efficiently and with high specificity."

It’s the bottom paragraph of page 19 of the fully enclosed provisional. Please note that it was page 45 of Fu’s grant application, which was the 7th page faxed to Illumina on 02/07/2000 at 11:29 from the phone number 1-619-587-4297.

The last page of the application includes a slide with the UCSD logo clearly states in the Figure: “Detection of Alternative Splicing on Zip-Code Arrays and Comparison with RT-PCR.” That means they already used bead arrays in their collaborative experiments, and clearly called them zip-code arrays.

This irrefutably shows:

1. That Fu was using the zip-codes on bead arrays with Illumina ... is there anyway you can subpoena

with Illumina — is there anyway you can subpoena Fu's lab at UCSD to get a list of those zip-codes he used in his experiments? Alternatively, you should also be able to get that list from Illumina.

2. Fu, correctly references Gerry 1999 in this application, on the very same page. Meanwhile, Fan deceitfully inserts a fake reference quoting a 1999 year, even though the document is already in 2000.

3. EVERY followup patent application in this series refuses to acknowledge Gerry's publication.

THUS: Illumina knowingly and deceitfully set out to defraud Cornell of royalties due form Barany's Zip code chemistry, ligase detection, and addressable arrays inventions.

The recent ruling against Regeneron and in favor of Amgen for the blatant infringement of Amgen's IP (Regenron's cholesterol-lowering drug Praluent, vs. the competing Amgen drug Repatha which inhibits KCSK9) is instructive.

The judge ruled that Regenron "“demonstrated irreparable harm” to Amgen and that money damages were inadequate compensation.”

Regeneron's market cap fell $2 billion.

We would like to introduce the concept that Illumina did “irreparable harm to Cornell” - in doing so causing Cornell to lose a leadership position in terms of prestige and ability to fund raise for cancer detection work. This irreparable harm still exists today in the form of Grail — the spinoff from Illumina announcing they are raising $1 billion for early detection of Cancer, knowing full well that is exactly what Barany's lab is developing at this time, as evidenced by 10-pages of probing during my deposition….

Again, key point is that to this day, 94% of Illumina's product still willfully infringe on Barany's IP.

Kindly acknowledge you have received this and the

following email…

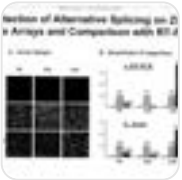
Best,

Francis

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

View less



IPR2014-01093, No. 58 Notice - Petitio…

60180810_Fan_Fu_02_07_2000.pdf

Subject Re: Privileged and Confidential: Detailed Case Summary and Strategic Alignment: Cornell and Akin Gump Only; Part 21

From Francis Barany <barany@med.cornell.edu>

To: Valerie Cross <vlc1@cornell.edu>, Pearson, Matthew <mpearson@AKINGUMP.com>, Weil, Jason <jweil@akingump.com>

Cc: Dianne Elderkin <delderkin@akingump.com>, Brian Kelly <bjk44@cornell.edu>, Monib Zirvi <matzirvi@yahoo.com>, Francis Barany <barany@med.cornell.edu>

Date Jan 7, 2017 at 2:14 PM

Dear Valerie, Matthew, and Jason,

Just to give you an additional perspective on why Illumina is panicking about the '269 and '373 patent, kindly find enclosed the US6913884 patent by Stuelpnagel & Chee, filed on August 16, 2001.

This application is a precursor to sequencing genomic DNA on a solid support.

It clearly uses Barany's LDR technology, see Figure 4 — which once again is willfully misleading…

Tellingly, they did not quote any Barany applications, and in fact, the first publication on the from top their patent application is our own "Khanna et al work — which was specifically cited by the examiner. In fact, it is the ONLY reference cited by the examiner.

This is very important, since this patent is the "missing link" between our claims in '269 and '373 and the NGS applications. Once again, Illumina's own patent applications show they willfully and deceitfully tried to hide that our technology is the

fundamental operating system for NGS — currently a multi-billion/year product for Illumina.

Would you kindly send Monib and myself the prosecution history of this patent?

Also I am going through the IPR case:

U.S. Patent No. 7,955,794
Ariosa Diagnostics, Inc. v. Illumina, Inc.

I noticed that the application was originally rejected by the patent examiner — who correctly cited the Barany patent(s). Illumina deceitfully told the examiner that the Barany technology could not be used for more than 50-100 probes, citing difficulties ABI had in developing the SNPlex assays. Illumina said the only way the problem could be solved was by capturing the DNA on a solid support.

However, ABI did not follow the teachings of Barany to use blocked downstream primers and exonuclease digestion. When such an approach is used — for example by Ron Davis in LDR-PCR with circularization — what he calls MIP probes (see enclosed publications), but what we already patented in US 7,556,924, there is no problem detecting 10,000 SNPs simultaneously, without resorting to capturing the genomic DNA on a solid support.

Very important. We (Monib and myself) need to see the prosecution history of the main Illumina patents filed by Chee, Fan, and Stuelpnagel.

We need to see how many times the examiner cited Barany IP (or Barany references as in the patent below), and Illumina was deceitful in response.

Do you already have that prosecution history?

If yes, would you kindly either email or set up a file transfer for Monib and myself to look at?

If not, would you kindly obtain that information ASAP?

Most appreciated,

Francis

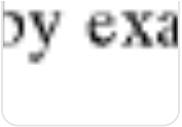
[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

United States Patent 7,556,924
Barany , et al. July 7, 2009
Detection of nucleic acid sequence differences using coupled ligase detection with padlock probes and polymerase chain reactions

Abstract
The present invention relates to a method for identifying a target nucleotide sequence. This method involves forming a ligation product on a target nucleotide sequence in a ligase detection reaction mixture, amplifying the ligation product to form an amplified ligation product in a polymerase chain reaction (PCR) mixture, detecting the amplified ligation product, and identifying the target nucleotide sequence. Such coupling of the ligase detection reaction and the polymerase chain reaction permits multiplex detection of nucleic acid sequence differences.

View less



US6913884_Stuelpnagel_Chee_08_16…

MIP_10,000_SNPs_parallele_2005.pdf

MIP_CoCA_copy_number_Parallele_20…

MIP_copy_quantif_parallele_2005.pdf

MIP_Parallele_Nature_Biotech_2003.pdf

Subject RE: Privileged and Confidential: Detailed Case Summary and Strategic Alignment: Cornell and Akin Gump Only; Part 10

From Weil, Jason <jweil@akingump.com>

To: Francis Barany <barany@med.cornell.edu>, Valerie Cross <vlc1@cornell.edu>, Pearson, Matthew <mpearson@AKINGUMP.com>

Cc: Elderkin, Dianne <delderkin@AKINGUMP.com>, Brian Kelly <bjk44@cornell.edu>, Monib Zirvi <matzirvi@yahoo.com>

Date Jan 7, 2017 at 6:49 PM

Hi Francis,

We received your emails.

Thanks,
Jason

From: Francis Barany [mailto:barany@med.cornell.edu]
Sent: Friday, January 06, 2017 6:48 PM
To: Valerie Cross; Pearson, Matthew; Weil, Jason
Cc: Elderkin, Dianne; Brian Kelly; Monib Zirvi; Francis Barany
Subject: Re: Privileged and Confidential: Detailed Case Summary and Strategic Alignment: Cornell and Akin Gump Only; Part 10
Importance: High

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Our research has led to a number of important questions below that need to be resolved

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Kindly find enclosed some additional sections of our master Powerpoint – we are not resending you older files (other than a review of summaries) you already have those from our emails to you on December 19th.

We are also sending supporting documentation of a series of patent applications by Fan, Fan & Chee, and Fan & Fu.

Further, because Illumina recently revamped their product lines on their web-site, we reanalyzed their product line, using stringent criteria for inclusion in the infringement category. Even we were shocked to see that 94% of their products infringed on Cornell's IP.* We will provide those documents in followup emails.

We are sending these files tonight to provide you some time to review prior to our Tuesday Phone meeting.

Kindly confirm receipt.

Best,

Francis & Monib

[redacted]
barany@med.cornell.edu

[redacted]

*(excluding rRNA removal kits).

---

1. Does Akin-Gump have access to the Affymetrix files – now that the company is part of ThermoFisher? Would you be able to find minutes of meetings where Mark Chee, Kevin Gunderson, and/or J.B. Fan were present during discussion between Mike Hunkapiller of ABI with Steve Fodor of Affymetrix concerning zip code arrays, which Affymetrix renamed "Tag Arrays"? Would you be able to find such files from the ABI side?

2. Did the discovery reveal documents from Illumina

where they refer to zip code sequences and Tag sequences in the same document? Further, are there additional documents where, "OLA" or "GoldenGate" are mentioned with "Illumacodes", "Tag sequences", "Adapter sequences", "Decoder Binding Ligands", and "Identifier Binding Ligands", or "Zipcode sequences".

3. How much can we bring in that some of the "co-inventors" are serial copycats, from Affymetrix, to Illumina, to Ariosa?

In fact Illumina is now suing Ariosa for IP:
- which Oliphant and Stuelpnagel took from Illumina,
- which Chee, Gunderson and Fan while at Illumina took from Affymetrix and Barany,
- which Fodor, Chee, Gunderson and Fan while at Affymetrix also took from Barany?

4. We developed the "addressable array", while Illumina only had randomly "assembled array". It wasn't until after Illumina got access to our zip code chemistry, that they could make their assembled arrays into addressable or universal arrays. If the arrays are not addressable, they will not work. Would you be able to determine when Illumina switched from the term "assembled array" to the term "address" and "addressable array" in their patents and internal documents?

5. In the trial, if it is known, can it be revealed if the 16 zip codes Illumina initially used were the original 16 Barany zip codes from our list? How will the Norman Gerry Patent or Paper with these sequences in them be introduced or presented at trial?

6. Illumina says 1536 – 16 = 1520 zipcodes worked in their US7226734 patent, same number as Gunderson et al. 2004 paper. Matthew, do you know if any of the 16 zip codes removed were the Barany 16 zip codes? Did they really fail to have 16 zip codes working, or did they deliberately mislead as to hide the true nature of what they did?

7. During the Ariosa-Illumina IPR, Stuelpnagel's deposition from the Zebala/Syntrix suit was presented. Is there any way to introduce the Ariosa – Illumina IPR and use any of the testimony at trial? (e.g. claim construction on "solid support"). If Zebala/Syntrix is

construction on "solid support"). If Zebula/Synthx is even accidentally or inadvertently introduced by witnesses at our trial, will it be considered prejudicial and possible grounds for appeal or will the judge ask the jury to disregard it?

8. Walt and Chee played critical roles at Illumina. Chee attempted to file or filed numerous patents and Walt played an important supervisory and scientific role. Walt was mentioned by name in a provisional patent application which included reference to our original zip code chemistry and Universal zip code arrays. Can the fact that Walt and Chee did not appear in their defense be presented? Wouldn't it look like a tacit/implied admission of guilt on the part of the defendant?

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Subject Re: Privileged and Confidential: Detailed Case Summary and Strategic Alignment: Cornell and Akin Gump Only; Part 10

From Francis Barany <barany@med.cornell.edu>

To: Weil, Jason <jweil@akingump.com>

Cc: Valerie Cross <vlc1@cornell.edu>, Pearson, Matthew <mpearson@AKINGUMP.com>, Elderkin, Dianne <delderkin@AKINGUMP.com>, Brian Kelly <bjk44@cornell.edu>, Monib Zirvi <matzirvi@yahoo.com>

Date Jan 7, 2017 at 7:19 PM

Dear Jason,

Thanks — including the two I sent today from my home computer?

Best,

Francis

[redacted]

barany@med.cornell.edu

[redacted]

> On Jan 7, 2017, at 6:49 PM, Weil, Jason <jweil@akingump.com> wrote:
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> Hi Francis,
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Sent: Friday, January 06, 2017 6:48 PM
To: Valerie Cross; Pearson, Matthew; Weil, Jason
Cc: Elderkin, Dianne; Brian Kelly; Monib Zirvi; Francis Barany
Subject: Re: Privileged and Confidential: Detailed Case Summary and Strategic Alignment: Cornell and Akin Gump Only; Part 10
Importance: High

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Subject RE: Privileged and Confidential: Detailed Case Summary and Strategic Alignment: Cornell and Akin Gump Only; Part 10

From Weil, Jason <jweil@akingump.com>

To: barany@med.cornell.edu <barany@med.cornell.edu>

Cc: Elderkin, Dianne <delderkin@AKINGUMP.com>, bjk44@cornell.edu <bjk44@cornell.edu>, matzirvi@yahoo.com <matzirvi@yahoo.com>, Pearson, Matthew <mpearson@AKINGUMP.com>, vlc1@cornell.edu <vlc1@cornell.edu>

Date Jan 7, 2017 at 7:52 PM

Yep, we got those as well.

Thanks

-----Original Message-----
From: Francis Barany [barany@med.cornell.edu]
Received: Saturday, 07 Jan 2017, 7:19PM
To: Weil, Jason [jweil@akingump.com]
CC: Valerie Cross [vlc1@cornell.edu]; Pearson, Matthew [mpearson@AKINGUMP.com]; Elderkin, Dianne [delderkin@AKINGUMP.com]; Brian Kelly [bjk44@cornell.edu]; Monib Zirvi [matzirvi@yahoo.com]
Subject: Re: Privileged and Confidential: Detailed Case Summary and Strategic Alignment: Cornell and Akin Gump Only; Part 10

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[redacted]

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Jason

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Sent: Friday, January 06, 2017 6:48 PM
To: Valerie Cross; Pearson, Matthew; Weil, Jason
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Subject Re: Privileged and Confidential: Detailed Case Summary and Strategic Alignment: Cornell and Akin Gump Only; Part 22

From Francis Barany <barany@med.cornell.edu>

To: Valerie Cross <vlc1@cornell.edu>, Pearson, Matthew <mpearson@AKINGUMP.com>, Weil, Jason <jweil@akingump.com>

Cc: Elderkin, Dianne <delderkin@AKINGUMP.com>, bjk44@cornell.edu <bjk44@cornell.edu>, Monib Zirvi <matzirvi@yahoo.com>, Francis Barany <barany@med.cornell.edu>

Date Jan 8, 2017 at 2:15 PM

Dear Valerie, Matthew, and Jason,

We apologize for these 2 additional emails, but we believe this latest set of documents will make your life a lot easier.

We downloaded the transcripts from John Zebala's Syntrix vs. Illumina case, and have been going over them this weekend. Many of the documents we need to see are sealed, and some are only available through Illumina — such as a scanning electron micrograph of their BeadArray surface. It is now eminently clear WHY they wanted all these documents sealed, and why they put a gag order on Zebala NOT to communicate with Cornell.

Syntrix Biosystems, Inc. v. Illumina, Inc., 3:10cv05870-BHS

1. Document 292, pg 190. John Zebala credits Barany for developing LCR and Universal DNA microarrays.

2. Document 292, pg 322. John Zebala credits Barany for introducing Zebala to ABI.

3. Document 292, pg 325. Deal between ABI and Syntrix falls apart because Affymetrix publishes patent that claims to use PNA in Arrays. This information was stolen from our 1994 NCI grant application. I believe that John brought this patent to Cornell's attention, and it was successfully overturned.

4. Document 292, pg 342. Mention is made that Illumina's arrays are porous coatings, (infringing on Zebala's '682 patent), also mentions Joe Smith — this is what Illumina tried to subpoena FB on August 9, 2012, and Valerie successfully countered the subpoena.

5. Document 292, pg 344 & 345. Zebala visits Illumina's website where they call their product "Sentrix Arrays". Zebala pulls out calculator and dramatically announces odds are 1 in 8-billion they could pick that name randomly…

Please stay tuned for next email...

Best,

Francis & Monib

[redacted]

barany@med.cornell.edu

[redacted]

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Syntrix Biosystems, Inc. v. Illumina Inc, …

Subject Re: Privileged and Confidential: Detailed Case Summary and Strategic Alignment: Cornell and Akin Gump Only; Part 23

From Francis Barany <barany@med.cornell.edu>

To: Valerie Cross <vlc1@cornell.edu>, Pearson, Matthew <mpearson@AKINGUMP.com>, Weil, Jason <jweil@akingump.com>

Cc: Elderkin, Dianne <delderkin@AKINGUMP.com>, bjk44@cornell.edu <bjk44@cornell.edu>, Monib Zirvi <matzirvi@yahoo.com>, Francis Barany <barany@med.cornell.edu>

Date Jan 8, 2017 at 2:17 PM

Dear Valerie, Matthew, and Jason,

With regards to Illumina's surface, putting beads in direct contact with a silicon-dioxide layer creates a contiguous surface, and as such Syntrix vs Illumina established that the silicon dioxide acts a polymeric binder with the silica beads to create a contiguous porous coating (surface) on a silicon wafer thus creating a gelled network of particles as a surface. This is an important precedent that needs to be used because our claim language clearly includes porous surfaces created using a variety of combinations of materials including silicon dioxide and silica.

Below is our own language from the '917 case, where you can clearly see that we have covered this composite combination from the words highlighted in red below.

Syntrix Biosystems, Inc. v. Illumina, Inc., 3:10cv05870-BHS

1. Document 294, pgs 566, 574, 575, 577: Michael L. Metzker, Ph.D., expert witness for Syntrix presented exhibit 460 which was a schematic

presented exhibit 460 which was a schematic diagram of 1, 2, &3 micron bead arrays (List of exhibits is enclosed, however, Exhibit 460 was sealed). Description shows that the SiO2 layer is grown, and the beads are contiguous with that layer. The SiO2 acts as a “polymeric binder” which creates a porous-composite surface. The surface is described as comprised of particles, beads, spheres...

2. Document 294, pas 670, 671: Introduces “Dickinson et al.” provisional patents (US6770441 enclosed as an example, however, I did not download the original filing) which more closely represents the current Illumina Infinium BeadArray chips. This is important because these arrays are essentially porous surfaces that unambiguously follow the teachings of the ‘917 application.

3. The case mentioned the “Seul US7749774” application, filed 04, 25, 1996 — two months after our zip code array filing — multiple times. Metzker would also help with explaining its relevance.

Question: Would you be able to retain Michael L. Metzker, Ph.D. as an expert witness on solid surfaces for our side? I know of his scientific work on reversible terminators, and it is superb, and he clearly knows everything about the structure of Illumina products.

His mini-bio and contact information is below.

Looking forward to our conversation on Tuesday,

Best,

Francis & Monib

[redacted]

barany@med.cornell.edu

[redacted]

———————

Michael L. Metzker Ph.D.

Dr. Michael L. Metzker, Ph.D. is the Founder of LaserGen, Inc. and served as its Chief Executive Officer, President and Chief Technology Officer. Dr. Metzker has over 20 years of experience in the biotechnology and pharmaceutical industries, as well as with leading academic institutions. He is currently an Associate Professor of Genetics at Baylor College of Medicine, and an Adjunct Assistant Professor of Chemistry at Rice University. Dr. Metzker has served as an expert witness for several HIV criminal cases, presenting a breakthrough method of phylogenetic analysis of HIV-1 DNA sequences. During his career, he has held senior-level research positions with Merck Research Laboratories and Applied Biosystems. Dr. Metzker served as Chairman of LaserGen, Inc. and serves as its Director. He has published over 30 research papers in leading scientific journals, authored numerous book chapters, and obtained multiple patents. Dr. Metzker received his B.S. from the University of California at Davis (1984) and his Ph.D. from Baylor College of Medicine in Houston, TX (1996).

Michael L. Metzker, Ph.D.
Associate Professor
Baylor College of Medicine
Human Genome Sequencing Center
Department of Molecular & Human Genetics
One Baylor Plaza, N1409
Houston, TX 77030
(713) 798-7565
(713) 798-5741 (fax)
mmetzker@bcm.edu

———————

United States Patent 7,083,917

Barany , et al. August 1, 2006

Detection of nucleic acid sequence differences using the ligase detection reaction with addressable arrays

...

The solid support can be made from a wide variety

of materials. The substrate may be biological, nonbiological, organic, inorganic, or a combination of any of these, existing as particles, strands, precipitates, gels, sheets, tubing, spheres, containers, capillaries, pads, slices, films, plates, slides, discs, membranes, etc. The substrate may have any convenient shape, such as a disc, square, circle, etc. The substrate is preferably flat but may take on a variety of alternative surface configurations. For example, the substrate may contain raised or depressed regions on which the synthesis takes place. The substrate and its surface preferably form a rigid support on which to carry out the reactions described herein. The substrate and its surface is also chosen to provide appropriate light-absorbing characteristics. For instance, the substrate may be a polymerized Langmuir Blodgett film, functionalized glass, Si, Ge, GaAs, GaP, SiO.sub.2, SiN.sub.4, modified silicon, or any one of a wide variety of gels or polymers such as (poly)tetrafluoroethylene, (poly)vinylidenedifluoride, polystyrene, polycarbonate, polyethylene, polypropylene, polyvinyl chloride, poly(methyl acrylate), poly(methyl methacrylate), or combinations thereof. Other substrate materials will be readily apparent to those of ordinary skill in the art upon review of this disclosure. In a preferred embodiment, the substrate is flat glass or single-crystal silicon.

According to some embodiments, the surface of the substrate is etched using well known techniques to provide for desired surface features. For example, by way of the formation of trenches, v-grooves, mesa structures, raised platforms, or the like, the synthesis regions may be more closely placed within the focus point of impinging light, be provided with

reflective "mirror" structures for maximization of light collection from fluorescent sources, or the like.

Surfaces on the solid substrate will usually, though not always, be composed of the same material as the substrate. Thus, the surface may be composed of any of a wide variety of materials, for example, polymers, plastics, ceramics, polysaccharides, silica or silica-based materials, carbon, metals, inorganic glasses, membranes, or composites thereof. The

surface is functionalized with binding members which are attached firmly to the surface of the substrate. Preferably, the surface functionalities will be reactive groups such as silanol, olefin, amino, hydroxyl, aldehyde, keto, halo, acyl halide, or carboxyl groups. In some cases, such functionalities preexist on the substrate. For example, silica based materials have silanol groups, polysaccharides have hydroxyl groups, and synthetic polymers can contain a broad range of functional groups, depending on which monomers they are produced from. Alternatively, if the substrate does not contain the desired functional groups, such groups can be coupled onto the substrate in one or more steps.

…

One approach to applying functional groups on a silica-based support surface is to silanize with a molecule either having the desired functional group (e.g., olefin, amino, hydroxyl, aldehyde, keto, halo, acyl halide, or carboxyl) or a molecule A able to be coupled to another molecule B containing the desired functional group. In the former case, functionalizing of glass- or silica-based solid supports with, for example, an amino group is carried out by reacting with an amine compound such as 3-aminopropyl triethoxysilane, 3-aminopropylmethyldiethoxysilane, 3-aminopropyl dimethylethoxysilane, 3-aminopropyl trimethoxysilane, N-(2-aminoethyl)-3-aminopropylmethyl dimethoxysilane, N-(2-aminoethyl-3-aminopropyl) trimethoxysilane, aminophenyl trimethoxysilane, 4-aminobutyldimethyl methoxysilane, 4-aminobutyl triethoxysilane,

aminoethylaminomethyphenethyl trimethoxysilane, or mixtures thereof. In the latter case, molecule A preferably contains olefinic groups, such as vinyl, acrylate, methacrylate, or allyl, while molecule B contains olefinic groups and the desired functional groups. In this case, molecules A and B are polymerized together. In some cases, it is desirable to modify the silanized surface to modify its properties (e.g., to impart biocompatibility and to increase mechanical stability). This can be achieved by addition of olefinic molecule C along with molecule B to produce a polymer network containing molecules A, B, and C

molecules A, B, and C.

Example 1

Immobilization of capture oligonucleotides to solid supports

The solid support for immobilization was glass, in particular microscope slides The immobilization to glass (e.g., microscope slides), or other supports such as silicon (e.g., chips), membranes (e.g., nylon membranes), beads (e.g., paramagnetic or agarose beads), or plastics supports (e.g., polyethylene sheets) of capture oligonucleotides in spatially addressable arrays is comprised of 5 steps:

A. Silanization of Support

The silanization reagent was 3-aminopropyl triethoxysilane ("APTS"). Alternatively, 3-glycidoxypropyltrimethoxysilane. (K. L. Beattie, et al., "Advances in Genosensor Research," Clin. Chem., 41:700 706 (1995); U. Maskos, et al., "Oligonucleotide Hybridizations on Glass Supports: a Novel Linker for Oligonucleotide Synthesis and Hybridization Properties of Oligonucleotides Synthesized in situ, "Nucleic Acids Res., 20:1679 1684 (1992); C. F. Mandenius, et al., "Coupling of Biomolecules to Silicon Surfaces for Use in

Ellipsometry and Other Related Techniques," Methods Enzymol., pp. 388 394 (1988), which are hereby incorporated by reference) or 3-(trimethoxysilyl)propyl methacrylate (M. Glad, et al., "Use of Silane Monomers for Molecular Imprinting and Enzyme Entrapment in Polysiloxane-coated Porous Silica," J. Chromatogr. 347:11 23 (1985); E. Hedborg, et al., "Some Studies of Molecularly-imprinted Polymer Membranes in Combination with Field-effect Devices," Sensors and Actuators A 37 38:796 799 (1993); and M. Kempe, et al., "An Approach Towards Surface Imprinting Using the Enzyme Ribonuclease A," J. Mol. Recogn. 8:35 39 (1995), which are hereby incorporated by reference) can be used as an initial silanization reagent. Prior

to silanization, the support was cleansed and the surface of the support was rendered hydrophobic. Glass slides (Fisher Scientific, Extra thick microslides, frosted cat.# 12-550-11) were incubated in conc. aq. NH.sub.4OH--H.sub.2O.sub.2--H.sub.2O (1:1:5, v/v/v) at 80.degree. C. for 5 min and rinsed in distilled water. The support was then washed with distilled water, ethanol and acetone as described in the literature (C. F. Mandenius, et al., "Coupling of Biomolecules to Silicon Surfaces for Use in Ellipsometry and Other Related Techniques," Methods Enzymol., pp. 388 394 (1988); Graham, et al., "Gene Probe Assays on a Fibre-Optic Evanescent Wave Biosensor," Biosensors & Bioelectronics, 7: 487 493 (1992); Jonsson, et al., "Adsorption Behavior of Fibronectin on Well Characterized Silica Surfaces," J. Colloid Interface Sci., 90:148 163 (1982), which are hereby incorporated by reference). The support was silanized overnight at room temperature in a solution of 2% (v/v) 3-aminopropyl triethoxysilane (Sigma, St. Louis, Mo.) in dry acetone (99.7%) (modified after Z. Guo, et. al., "Direct Fluorescence Analysis of Genetic Polymorphisms by Hybridization with Oligonucleotide Arrays on Glass Supports," Nucl. Acids Res. 22:5456 65 (1994), which is hereby incorporated by reference). The support was then thoroughly washed in dry acetone and dried at 80.degree. C. in a vacuum desiccator.

B. Derivatization of Silanized Solid Support with Functional Groups (e.g., Carboxyl or Amino Groups)

When the silanization reagent was APTS, the desired amino functionality was introduced directly. Other functional groups can be introduced, either by choosing an appropriate silanization reagent primer that already contains the functional group (e.g., 3-(trimethoxysilyl)propyl methacrylate to functionalize the surface with a polymerizable acrylate, (M. Glad, et al., "Use of Silane Monomers Imprinting and Enzyme Entrapment in Polysiloxane-coated Porous Silica," J. Chromatogr. 347:11 23 (1985); E. Hedborg, et al., "Some Studies of Molecularly-imprinted Polymer Membranes in Combination with

Field-effect Devices," Sensors and Actuators A 37 38:796 799 (1993); and M. Kempe, et al., "An Approach Towards Surface Imprinting Using the Enzyme Ribonuclease A," J. Mol. Recogn. 8:35 39 (1995), which are hereby incorporated by reference), or by reacting the amino-functionalized surface with a reagent that contains the desired functional group (e.g., after localized light-directed photodeprotection of protected amino groups used in photolithography, (Fodor, et al., "Light-Directed, Spatially Addressable Parallel Chemical Synthesis," Science, 251:767 773 (1991); Fodor, et al., "Multiplexed Biochemical Assays with Biological Chips," Nature, 364:555 556 (1993), which are hereby incorporated by reference)).

View less

Syntrix Biosystems, Inc. v. Illumina Inc, …

Syntrix Biosystems, Inc. v. Illumina Inc, …

US6770441_Illumina_Array_compositio…

US7749774_Seul_filed_04_25_1996.pdf

Subject Fwd: (Forward to others) WebEx meeting invitation: Illumine Case - Pearson

From Francis Barany <barany@med.cornell.edu>

To: Pearson, Matthew <mpearson@AKINGUMP.com>, Valerie Cross <vlc1@cornell.edu>

Cc: Weil, Jason <jweil@akingump.com>, Monib Zirvi <matzirvi@yahoo.com>, Francis Barany <barany@med.cornell.edu>

Date Jan 10, 2017 at 12:04 PM

Dear Matthew and Valerie,

Matthew, great talking today.

Valerie, we have a followup on Friday @ 10:00 AM if you would like to join.

If that time does not work for you, would you please let us know some time in the afternoon that would work for you?

Monib and I would call you then and update you. We really would like to speak with you about the case and Cornell's overall strategy.

Best!

Francis

[redacted]
barany@med.cornell.edu

[redacted]

Begin forwarded message:

From: Francis Barany <messenger@webex.com>
Subject: (Forward to others) WebEx meeting invitation: Illumine Case - Pearson
Date: January 10, 2017 at 12:00:05 PM EST
To: <barany@med.cornell.edu>
Reply-To: <barany@med.cornell.edu>

You can forward this invitation to others.
Hello,

Francis Barany invites you to join this WebEx meeting.

Illumine Case - Pearson
Friday, January 13, 2017
10:00 am | Eastern Standard Time (New York, GMT-05:00) | 1 hr
Meeting number (access code): [redacted]
Meeting password: [redacted]

Add to Calendar

When it's time, join the meeting.

Join by phone
[redacted] Call-in toll number (US/Canada)
Global call-in numbers

Can't join the meeting?

IMPORTANT NOTICE: Please note that this WebEx service allows audio and other information sent during the session to be recorded, which may be discoverable in a legal matter. By joining this session, you automatically consent to such recordings. If you do not consent to being recorded, discuss your concerns with the host or do not join the session.

Subject Re: (Forward to others) WebEx meeting invitation: Illumine Case - Pearson

From Valerie Cross Dorn <vlc1@cornell.edu>

To: Francis Barany <barany@med.cornell.edu>

Cc: Matt Pearson <mpearson@AKINGUMP.com>, Jason Weil <jweil@AKINGUMP.com>, Monib Zirvi <matzirvi@yahoo.com>

Date Jan 10, 2017 at 2:28 PM

10 on Friday works for me. I had a staff meeting today that ran very late so I could not join your discussion, but will look forward to the follow-up on Friday. Valerie

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> Best!
>
> Francis
>
> [redacted]
> barany@med.cornell.edu
>
> [redacted]
>
> > Begin forwarded message:
> >
> > **From:** Francis Barany <messenger@webex.com>

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Date: January 10, 2017 at 12:00:05 PM EST
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<WebEx_Meeting.ics>

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Subject Re: (Forward to others) WebEx meeting invitation: Illumina Case - Pearson

From Francis Barany <barany@med.cornell.edu>

To: Valerie Cross <vlc1@cornell.edu>

Cc: Matt Pearson <mpearson@AKINGUMP.com>, Jason Weil <jweil@AKINGUMP.com>, Monib Zirvi <matzirvi@yahoo.com>

Date Jan 10, 2017 at 2:49 PM

Dear Valerie,

Terrific, we hope to have a tightly honed message for you by then.

(Matthew gave me some suggestions on what to focus on this morning.)

Best,

Francis

[redacted]
barany@med.cornell.edu

[redacted]

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[redacted]
barany@med.cornell.edu

[redacted]

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<WebEx_Meeting.ics>

View less

Subject Privileged and Confidential: Followup to January 10th phone meeting

From Francis Barany <barany@med.cornell.edu>

To: Pearson, Matthew <mpearson@AKINGUMP.com>, Weil, Jason <jweil@akingump.com>

Cc: Valerie Cross <vlc1@cornell.edu>, Francis Barany <barany@med.cornell.edu>, Monib Zirvi <matzirvi@yahoo.com>

Date Jan 12, 2017 at 2:15 PM

Dear Matthew,

Good talking on Tuesday, and looking forward to our discussion tomorrow @ 10:00 AM.

As discussed, if you can find the original filing of the Canadian version of the patent application at the end of this email (CA 2399733 C), that would help, as it's the only one in this series with an abstract that reads almost word-for-word as our IP.

This Series of 3 patents was filed by Fan, one by himself, another with Chee, another with Fu, all on the same date of Feb 7, 2001. They all go back to the fateful submission of Feb. 7, 2000 where Illumina did not include Fu as a co-inventor on the application, even though it was his grant application.

Also, as we discussed, the prosecution history of one of these patents claimed Barany as prior art, and Fan gave some explanation about needing to capture everything on a solid support in order to get it to work. However, we and others got it to work just fine in liquid…

How many other times did the prosecution history of the patents listed below refer to Barany's IP as prior

art?

Are you able to see the prosecution history for a

Are you able to see the prosecution history for a patent that didn't issue?

If yes, kindly include:

US20030096239_Gunderson_Chee_Zipcode_2003
US20050074787_Universal_Array_Fan_Affy_1999_2005
US20030104434_Fan_Fu_Fig_1-18_08_09_2002
US20020132241_Fan_St_Chee_Fig_1-12W_07_24_2001

One of the unnerving things we've uncovered is that to this day, Illumina is still getting patents issued that use our Universal Array zip-code technology (although they call them "adapters") where they try to reach back to earlier filings from 1999, in an attempt to retroactively prove they invented it on their own — when in fact they stole it from Cornell. Often, they shuffle inventor order to confuse the law. One such example that we had missed previously is provided below. They even use the words "Universal Array" in the abstract.

Would you kindly email Monib and myself the prosecution history, so we can do the appropriate homework? I am not asking you or Jason to download all types of new information, but I am sure you already have the prosecution history for the relevant patents in the relevant time period.

Most appreciated,

Francis

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

United States Patent 9,279,148
Gunderson , et al. March 8, 2016
Detection of nucleic acid reactions on bead arrays

Abstract
The present invention is directed to methods and compositions for the use of micro sphere arrays to detect and quantify a number of nucleic acid reactions. The invention finds use in genotyping, i.e. the determination of the sequence of nucleic acids, particularly alterations such as nucleotide substitutions (mismatches) and single nucleotide polymorphisms (SNPs). Similarly, the invention finds use in the detection and quantification of a nucleic acid target using a variety of amplification techniques, including both signal amplification and target amplification. The methods and compositions of the invention can be used in nucleic acid sequencing reactions as well. All applications can include the use of adapter sequences to allow for universal arrays.

Inventors: Gunderson; Kevin (Encinitas, CA), Stuelpnagel; John R. (Encinitas, CA), Chee; Mark S. (Encinitas, CA), Fan; Jian-Bing (San Diego, CA)
Applicant:
Name City
State Country
Type

Illumina, Inc.
San Diego
CA
US
Assignee: Illumina, Inc. (San Diego, CA)
Family ID: 46322769
Appl. No.: 13/913,922
Filed: June 10, 2013

I apologize in advance if there is overlap among the lists...

1. Walt & Chee

	PAT. NO.		Title
1	9,163,283	T	Combinatorial decoding of random nucleic acid arrays
2	8,563,246	T	Combinatorial decoding of random nucleic acid arrays
3	8,206,917	T	Combinatorial decoding of random nucleic acid arrays
4	7,960,119	T	Combinatorial decoding of random nucleic acid arrays
5	7,563,576	T	Combinatorial decoding of random nucleic acid arrays
6	7,166,431	T	Combinatorial decoding of random nucleic acid arrays

7 6,620,584 T Combinatorial decoding of random nucleic acid arrays

2. Chee and Illumina

	PAT. NO.		Title
16	8,460,865	T	Multiplex decoding of array sensors with microspheres
17	8,288,103	T	Multiplex nucleic acid reactions
18	8,206,917	T	Combinatorial decoding of random nucleic acid arrays
20	8,003,354	T	Multiplex nucleic acid reactions
21	7,960,119	T	Combinatorial decoding of random nucleic acid arrays
22	7,955,794	T	Multiplex nucleic acid reactions
27	7,582,420	T	Multiplex nucleic acid reactions
28	7,563,576	T	Combinatorial decoding of random nucleic acid arrays
29	7,510,841	T	Methods of making and using composite arrays for the detection of a plurality of target analytes
30	7,455,971	T	Multiplex decoding of array sensors with microspheres
31	7,226,734	T	Multiplex decoding of array sensors with microspheres
32	7,166,431	T	Combinatorial decoding of random nucleic acid arrays
33	7,060,431	T	Method of making and decoding of array sensors with microspheres
34	7,033,754	T	Decoding of array sensors with microspheres
35	6,998,274	T	Composite arrays utilizing microspheres
37	6,913,884	T	Compositions and methods for repetitive use of genomic DNA
38	6,890,764	T	Encoding and decoding of array sensors utilizing nanocrystals
39	6,890,741	T	Multiplexed detection of analytes
40	6,858,394	T	Composite arrays utilizing microspheres
42	6,620,584	T	Combinatorial decoding of random nucleic acid arrays
43	6,544,732	T	Encoding and decoding of array sensors utilizing nanocrystals
44	6,429,027	T	Composite arrays utilizing microspheres
46	6,355,431	T	Detection of nucleic acid amplification reactions using bead arrays

3. Fan and Illumina

	PAT. NO.		Title
1	9,441,267	T	Detection of nucleic acid reactions on bead arrays
2	9,279,148	T	Detection of nucleic acid reactions on bead arrays
4	8,906,626	T	Multiplex nucleic acid reactions
6	8,288,103	T	Multiplex nucleic acid reactions
11	8,003,354	T	Multiplex nucleic acid reactions
12	7,955,794	T	Multiplex nucleic acid reactions

15 7,611,869 T Multiplexed methylation detection methods

16 7,582,420 T Multiplex nucleic acid reactions

17 7,361,488 T Nucleic acid detection methods using universal priming

18 6,890,741 T Multiplexed detection of analytes

19 6,812,005 T Nucleic acid detection methods using universal priming

4. Gunderson and Illumina

PAT. NO.		Title
19 8,486,625	T	Detection of nucleic acid reactions on bead arrays
21 8,412,467	T	Nucleic acid sequencing system and method
22 8,315,817	T	Independently removable nucleic acid sequencing system and method
23 8,244,479	T	Nucleic acid sequencing system and method using a subset of sites of a substrate
25 7,835,871	T	Nucleic acid sequencing system and method
26 7,670,810	T	Methods and compositions for whole genome amplification and genotyping
27 6,355,431	T	Detection of nucleic acid amplification reactions using bead arrays

— — — — — — — — — —

Nucleic acid detection methods using universal priming

CA 2399733 C

Publication number	CA2399733 C
Publication type	Grant
Application number	CA 2399733
PCT number	PCT/US2001/004056
Publication date	Sep 20, 2011
Filing date	Feb 7, 2001
Priority date	Feb 7, 2000
Also published as	CA2399733A1, DE60136166D1, DE60143723D1, EP1259643A2, EP1259643B1, EP1990428A1, EP1990428B1, US6890741, US20020006617, US20020132241,

US20030003490, US20040224352, US20040224353, WO2001057269A2, WO2001057269A3, Less «

Inventors Jian-Bing Fan, Mark S. Chee

Applicant Illumina, Inc., Jian-Bing Fan, Mark S. Chee

Export Citation BiBTeX, EndNote, RefMan

Classifications (25), Legal Events (1)

ABSTRACT

A method of determining the identification of nucleotides at detection positions in target sequences comprising: a) providing a plurality of probe sets, wherein each set comprises: i) a first ligation probe comprising an upstream universal priming site and a first target-specific sequence; and ii) a second ligation probe comprising a downstream universal priming site and a second target-specific sequence; wherein either the first or second target-specific sequence comprises a base at an interrogation position, and wherein at least one of said first and second ligation probes comprises an adapter sequence complementary to a capture probe on an array; b) hybridizing said plurality of probe sets to target sequences immobilized on a support or supports, said target sequences each comprising a target domain comprising a detection position and a second target domain adjacent to said detection position, wherein a first ligation probe comprising a sequence specific for the target hybridizes to one target domain and a

second ligation probe comprising a sequence specific for the target hybridizes to the other target domain, and wherein if said base at said interrogation position is perfectly complementary to a nucleotide at said detection position, a ligation complex is formed; c) providing a ligase that ligates said first and second ligation probes to form ligated probes; d) amplifying said ligated probes to generate a plurality of amplicons; e) contacting said amplicons with an array comprising capture probes on a solid support; and f) determining the nucleotide at each of said detection positions.

Subject RE: Privileged and Confidential: Followup to January 10th phone meeting

From Pearson, Matthew <mpearson@AKINGUMP.com>

To: Francis Barany <barany@med.cornell.edu>, Weil, Jason <jweil@akingump.com>

Cc: Valerie Cross <vlc1@cornell.edu>, Monib Zirvi <matzirvi@yahoo.com>

Date Jan 12, 2017 at 5:03 PM

Received – we can talk tomorrow.

From: Francis Barany [mailto:barany@med.cornell.edu]
Sent: Thursday, January 12, 2017 2:15 PM
To: Pearson, Matthew; Weil, Jason
Cc: Valerie Cross; Francis Barany; Monib Zirvi
Subject: Privileged and Confidential: Followup to January 10th phone meeting
Importance: High

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Also, as we discussed, the prosecution history of one of these patents claimed Barany as prior art, and Fan gave

these patents claimed Barany as prior art, and Fan gave some explanation about needing to capture everything on a solid support in order to get it to work. However, we and others got it to work just fine in liquid…

How many other times did the prosecution history of the patents listed below refer to Barany's IP as prior art?

Are you able to see the prosecution history for a patent that didn't issue?

If yes, kindly include:

US20030096239_Gunderson_Chee_Zipcode_2003
US20050074787_Universal_Array_Fan_Affy_1999_2005
US20030104434_Fan_Fu_Fig_1-18_08_09_2002
US20020132241_Fan_St_Chee_Fig_1-12W_07_24_2001

One of the unnerving things we've uncovered is that to this day, Illumina is still getting patents issued that use our Universal Array zip-code technology (although they call them "adapters") where they try to reach back to earlier filings from 1999, in an attempt to retroactively prove they invented it on their own — when in fact they stole it from Cornell. Often, they shuffle inventor order to confuse the law. One such example that we had missed previously is provided below. They even use the words "Universal Array" in the abstract.

Would you kindly email Monib and myself the prosecution history, so we can do the appropriate homework? I am not asking you or Jason to download all types of new information, but I am sure you already have the prosecution history for the relevant patents in the relevant time period.

Most appreciated,

Francis

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

_____

United States Patent 9,279,148
Gunderson , et al. March 8, 2016
Detection of nucleic acid reactions on bead arrays

Abstract
The present invention is directed to methods and compositions for the use of micro sphere arrays to detect and quantify a number of nucleic acid reactions. The invention finds use in genotyping, i.e. the determination of the sequence of nucleic acids, particularly alterations such as nucleotide substitutions (mismatches) and single nucleotide polymorphisms (SNPs). Similarly, the invention finds use in the detection and quantification of a nucleic acid target using a variety of amplification techniques, including both signal amplification and target amplification. The methods and compositions of the invention can be used in nucleic acid sequencing reactions as well. All applications can include the use of adapter sequences to allow for universal arrays.

Inventors: Gunderson; Kevin (Encinitas, CA), Stuelpnagel; John R. (Encinitas, CA), Chee; Mark S. (Encinitas, CA), Fan; Jian-Bing (San Diego, CA)
Applicant:
Name City
State Country
Type

Illumina, Inc.
San Diego
CA
US
Assignee: Illumina, Inc. (San Diego, CA)
Family ID: 46322769
Appl. No.: 13/913,922
Filed: June 10, 2013

I apologize in advance if there is overlap among the lists...

1. Walt & Chee

	PAT. NO.		Title
1	9,163,283	T	Combinatorial decoding of random

nucleic acid arrays

2 8,563,246 T Combinatorial decoding of random nucleic acid arrays

3 8,206,917 T Combinatorial decoding of random nucleic acid arrays

4 7,960,119 T Combinatorial decoding of random nucleic acid arrays

5 7,563,576 T Combinatorial decoding of random nucleic acid arrays

6 7,166,431 T Combinatorial decoding of random nucleic acid arrays

7 6,620,584 T Combinatorial decoding of random nucleic acid arrays

2. Chee and Illumina

PAT. NO.		Title
16 8,460,865	T	Multiplex decoding of array sensors with microspheres
17 8,288,103	T	Multiplex nucleic acid reactions
18 8,206,917	T	Combinatorial decoding of random nucleic acid arrays
20 8,003,354	T	Multiplex nucleic acid reactions
21 7,960,119	T	Combinatorial decoding of random nucleic acid arrays
22 7,955,794	T	Multiplex nucleic acid reactions
27 7,582,420	T	Multiplex nucleic acid reactions
28 7,563,576	T	Combinatorial decoding of random nucleic acid arrays
29 7,510,841	T	Methods of making and using composite arrays for the detection of a plurality of target analytes
30 7,455,971	T	Multiplex decoding of array sensors with microspheres
31 7,226,734	T	Multiplex decoding of array sensors with microspheres
32 7,166,431	T	Combinatorial decoding of random nucleic acid arrays
33 7,060,431	T	Method of making and decoding of array sensors with microspheres

34	7,033,754	T	Decoding of array sensors with microspheres
35	6,998,274	T	Composite arrays utilizing microspheres
37	6,913,884	T	Compositions and methods for repetitive use of genomic DNA
38	6,890,764	T	Encoding and decoding of array sensors utilizing nanocrystals
39	6,890,741	T	Multiplexed detection of analytes
40	6,858,394	T	Composite arrays utilizing microspheres
42	6,620,584	T	Combinatorial decoding of random nucleic acid arrays
43	6,544,732	T	Encoding and decoding of array sensors utilizing nanocrystals
44	6,429,027	T	Composite arrays utilizing microspheres
46	6,355,431	T	Detection of nucleic acid amplification reactions using bead arrays

3. Fan and Illumina

	PAT. NO.		Title
1	9,441,267	T	Detection of nucleic acid reactions on bead arrays
2	9,279,148	T	Detection of nucleic acid reactions on bead arrays
4	8,906,626	T	Multiplex nucleic acid reactions
6	8,288,103	T	Multiplex nucleic acid reactions
11	8,003,354	T	Multiplex nucleic acid reactions
12	7,955,794	T	Multiplex nucleic acid reactions
15	7,611,869	T	Multiplexed methylation detection methods
16	7,582,420	T	Multiplex nucleic acid reactions
17	7,361,488	T	Nucleic acid detection methods using universal priming
18	6,890,741	T	Multiplexed detection of analytes
19	6,812,005	T	Nucleic acid detection methods using universal priming

universal priming

4. Gunderson and Illumina

	PAT. NO.		Title
19	8,486,625	T	Detection of nucleic acid reactions on bead arrays
21	8,412,467	T	Nucleic acid sequencing system and method
22	8,315,817	T	Independently removable nucleic acid sequencing system and method
23	8,244,479	T	Nucleic acid sequencing system and method using a subset of sites of a substrate
25	7,835,871	T	Nucleic acid sequencing system and method
26	7,670,810	T	Methods and compositions for whole genome amplification and genotyping
27	6,355,431	T	Detection of nucleic acid amplification reactions using bead arrays

---

Nucleic acid detection methods using universal priming
CA 2399733 C

Publication number	CA2399733 C
Publication type	Grant
Application number	CA 2399733
PCT number	PCT/US2001/004056
Publication date	Sep 20, 2011
Filing date	Feb 7, 2001
Priority date	Feb 7, 2000
Also published as	CA2399733A1, DE60136166D1, DE60143723D1, EP1259643A2, EP1259643B1, EP1990428A1, EP1990428B1, US6890741, US20020006617, US20020132241, US20030003490, US20040224352, US20040224353, WO2001057269A2, WO2001057269A3, Less «
Inventors	Jian-Bing Fan, Mark S. Chee
Applicant	Illumina, Inc., Jian-Bing Fan, Mark S.

Chee

Export Citation BiBTeX, EndNote, RefMan

Classifications (25), Legal Events (1)

ABSTRACT

A method of determining the identification of nucleotides at detection positions in target sequences comprising: a) providing a plurality of probe sets, wherein each set comprises: i) a first ligation probe comprising an upstream universal priming site and a first target-specific sequence; and ii) a second ligation probe comprising a downstream universal priming site and a second target-specific sequence; wherein either the first or second target-specific sequence comprises a base at an interrogation position, and wherein at least one of said first and second ligation probes comprises an adapter sequence complementary to a capture probe on an array; b) hybridizing said plurality of probe sets to target sequences immobilized on a support or supports, said target sequences each comprising a target domain comprising a detection position and a second target domain adjacent to said detection position, wherein a first ligation probe comprising a sequence specific for the target hybridizes to one target domain and a second ligation probe comprising a sequence specific for the target hybridizes to the other target domain, and wherein if said base at said interrogation position is perfectly complementary to a nucleotide at said detection position, a ligation complex is formed; c) providing a ligase that ligates said first and second ligation probes to form ligated probes; d) amplifying said ligated probes to generate a plurality of amplicons; e) contacting said amplicons with an array comprising capture probes on a solid support; and f) determining the nucleotide at each of said detection positions.

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Subject Privileged

From Pearson, Matthew <mpearson@AKINGUMP.com>

To: 'George Barany' <barany@umn.edu>, Francis Barany (barany@med.cornell.edu) <barany@med.cornell.edu>, 'Robert Hammer' <rphammer@gmail.com>, 'Maria Kempe' <maria.kempe@med.lu.se>, 'Matthew Lubin' <lubingenetics@me.com>, 'Monib Zirvi' <matzirvi@yahoo.com>

Date Jan 13, 2017 at 9:40 AM

Privileged

Dear all –

I have attached a summary of the order we received this week from the judge in our case. Please let us know if you have any questions.

Happy New Year,
Matt Pearson

Matthew A. Pearson
AKIN GUMP STRAUSS HAUER & FELD LLP
[redacted] 19103-7013 | USA | Direct: +1 215.965.1258 | Internal: 21258
Fax: +1 215.965.1210 | mpearson@akingump.com | akingump.com | Bio

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2017-01-13 Memo to Inventors.pdf

Akin Gump
STRAUSS HAUER & FELD LLP

M E M O R A N D U M

ATTORNEY-CLIENT PRIVILEGED

January 13, 2017

To: Francis Barany, George Barany, Robert Hammer, Maria Kempe, Matthew Lubin, and Monib Zirvi

From: Akin Gump

Re: Claim Construction and Illumina's Motion to Amend

On January 10, 2017, Judge Stark issued an Order addressing our objections to the Report and Recommendation on Claim Construction issued by Magistrate Judge Thynge, as well as Illumina's Motion to Amend its Answer to plead inequitable conduct. We summarize the major points below.

Claim Construction

Judge Stark rejected some parts of Magistrate Judge Thynge's claim construction report and accepted others. Specifically, Judge Stark agreed with Cornell's construction of the term "solid support" and of all terms related to the linker and ways of attaching or coupling to the support. Judge Stark therefore rejected Magistrate Judge Thynge's report on that point.

Judge Stark accepted Illumina's construction of "capture oligonucleotide," all terms related to the 25% difference limitation, and "ligase detection reaction." Illumina will still maintain its arguments for these other elements. Although we would have obviously preferred that the Court adopt Cornell's proposed construction on all claim terms, we are very pleased that the Court agreed with our position for the solid support.

Illumina's proposed construction of solid support, which has now been rejected, required a "single-unitary substrate," And Illumina argued that its bead arrays did not meet that definition. The new construction adopted on Tuesday requires only a "solid-phase substrate." The change to the construction of solid support makes our argument more straightforward that bead arrays have solid supports.

Inequitable Conduct

Judge Stark also agreed that Illumina should not be able to argue that there was inequitable conduct during prosecution of the patents related to LDR-PCR.

ATTORNEY CLIENT PRIVILEGED
Francis Barany and Coinventors
Francis Barany, George Barany, Robert Hammer, Maria Kempe, Matthew Lubin, and Monib Zirvi
January 13, 2017
Page 2

To review, Illumina sought to add a defense that the LDR-PCR patents are unenforceable because of alleged inequitable conduct by the inventors and attorneys during prosecution of the patents. The sole basis for Illumina's claim was that a declaration filed during prosecution allegedly stated that the invention had been reduced to practice before a certain date, and that was not true. We argued that the declaration is, at worst, ambiguous, and that, in light of the other evidence showing that the inventors and prosecuting attorneys did not intend to deceive the Patent Office, Illumina would never be able to show that there was inequitable conduct.

A few months ago Magistrate Judge Thynge recommended that Illumina be permitted to amend its Answer to raise the inequitable conduct defense.

On Tuesday, Judge Stark rejected Magistrate Judge Thynge's recommendation and agreed with Cornell that, based on the evidence Illumina presented, Illumina would not be able to prove that the inventors or attorneys committed inequitable conduct. Accordingly, Judge Stark dismissed Illumina's motion and the question of inequitable conduct is no longer a part of the case.

We were very pleased with Judge Stark's ruling—he essentially agreed that Illumina's evidence that the prosecuting attorneys and inventors deceived the Patent Office was so insufficient that it would be futile for Illumina even to be permitted to raise inequitable conduct as a possible defense.

* * *

We do not expect that any of the above will significantly change the existing schedule/plans, and we will proceed as previously discussed. There is nothing that requires anyone's immediate attention, but we will be in touch over the coming months to the extent we need assistance in our trial preparation.

Subject Join WebEx meeting in progress:
Illumina Case - Pearson

From Francis Barany
<barany@med.cornell.edu>

To: mpearson@akingump.com
<mpearson@akingump.com>, Monib
Zirvi <matzirvi@yahoo.com>, Valerie
Cross <vlc1@cornell.edu>

Cc: Michael Goldman
<Michael.Goldman@leclairryan.com>,
Robert A. Buhrman
<buhrman@cornell.edu>, James J.
Mingle <james.mingle@cornell.edu>,
Francis Barany
<barany@med.cornell.edu>

Date Jan 13, 2017 at 9:57 AM

Subject Join WebEx meeting in progress: Illumina Case - Pearson

From Francis Barany <barany@med.cornell.edu>

To: mpearson@akingump.com <mpearson@akingump.com>, Monib Zirvi <matzirvi@yahoo.com>, Valerie Cross <vlc1@cornell.edu>

Cc: Michael Goldman <Michael.Goldman@leclairryan.com>, Robert A. Buhrman <buhrman@cornell.edu>, James J. Mingle <james.mingle@cornell.edu>, Francis Barany <barany@med.cornell.edu>

Date Jan 13, 2017 at 9:57 AM

My WebEx meeting is in progress. Please join.

Thanks!

Francis

[redacted]

barany@med.cornell.edu

[redacted]

Illumine Case - Pearson
Friday, January 13, 2017
10:00 am | Eastern Standard Time (New York, GMT-05:00) | 1 hr

Meeting number (access code): 645 027 175

Meeting password: Zipcode

Join Meeting
https://wcmc.webex.com/wcmc/e.php?
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MTID=mb776be406c958092722e35b20bd30f27d

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1-650-479-3207 Call-in toll number (US/Canada)

Global call-in numbers:
https://wcmc.webex.com/wcmc/globalcallin.php?serviceType=MC&ED=522616442&tollFree=0

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Subject Join WebEx meeting in progress: Illumina Case - Pearson

From Francis Barany <barany@med.cornell.edu>

To: mpearson@akingump.com <mpearson@akingump.com>, Monib Zirvi <matzirvi@yahoo.com>, Valerie Cross <vlc1@cornell.edu>

Cc: Michael Goldman <Michael.Goldman@leclairryan.com>, Robert A. Buhrman <buhrman@cornell.edu>, James J. Mingle <james.mingle@cornell.edu>, Francis Barany <barany@med.cornell.edu>

Date Jan 13, 2017 at 9:57 AM

My WebEx meeting is in progress. Please join.

Thanks!

Francis

[redacted]

barany@med.cornell.edu

[redacted]

Illumine Case - Pearson
Friday, January 13, 2017
10:00 am | Eastern Standard Time (New York, GMT-05:00) | 1 hr

Meeting number (access code): 645 027 175

Meeting password: Zipcode

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MTID=mb776be406c958092722e35b20bd30f27d

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https://wcmc.webex.com/wcmc/globalcallin.php?serviceType=MC&ED=522616442&tollFree=0

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Subject Join WebEx meeting in progress: Illumina Case - Pearson

From Francis Barany <barany@med.cornell.edu>

To: mpearson@akingump.com <mpearson@akingump.com>, Monib Zirvi <matzirvi@yahoo.com>, Valerie Cross <vlc1@cornell.edu>

Cc: Michael Goldman <Michael.Goldman@leclairryan.com>, Robert A. Buhrman <buhrman@cornell.edu>, James J. Mingle <james.mingle@cornell.edu>, Francis Barany <barany@med.cornell.edu>

Date Jan 13, 2017 at 9:57 AM

My WebEx meeting is in progress. Please join.

Thanks!

Francis

[redacted]

barany@med.cornell.edu

[redacted]

Illumine Case - Pearson
Friday, January 13, 2017
10:00 am | Eastern Standard Time (New York, GMT-05:00) | 1 hr

Meeting number (access code): 645 027 175

Meeting password: Zipcode

Join Meeting
https://wcmc.webex.com/wcmc/e.php?
MTID=mb776be406c95809272e35b20bd36f27d

MTID=mb776be406c958092722e35b20bd30f27d

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https://wcmc.webex.com/wcmc/globalcallin.php?serviceType=MC&ED=522616442&tollFree=0

Can't join the meeting?
https://help.webex.com/docs/DOC-5412

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Subject Re: Privileged and Confidential: Followup to January 13th phone meeting, Part 1

From Francis Barany <barany@med.cornell.edu>

To: Pearson, Matthew <mpearson@AKINGUMP.com>, Valerie Cross <vlc1@cornell.edu>

Cc: Weil, Jason <jweil@akingump.com>, Monib Zirvi <matzirvi@yahoo.com>, Goldman Mike <Michael.Goldman@leclairryan.com>, Brian Kelly <bjk44@cornell.edu>

Date Jan 13, 2017 at 5:13 PM

Dear Matthew and Valerie,

Thank you for listening this morning.

As promised, enclosed in this and the following emails are pdf's of the powerpoints (too large to send).

I will give Matthew the original powerpoint files on Tuesday, and then we will focus on the deposition.

Best,

Francis

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

> On Jan 12, 2017, at 5:03 PM, Pearson, Matthew <mpearson@AKINGUMP.com> wrote:
>
> Received. we can talk tomorrow

Received – we can talk tomorrow.

Cornell Illumina Case Overview Figures…

Subject Re: Privileged and Confidential: Followup to January 13th phone meeting, Part 2

From Francis Barany <barany@med.cornell.edu>

To: Pearson, Matthew <mpearson@AKINGUMP.com>, Valerie Cross <vlc1@cornell.edu>

Cc: Weil, Jason <jweil@akingump.com>, Monib Zirvi <matzirvi@yahoo.com>, Goldman Mike <Michael.Goldman@leclairryan.com>, Brian Kelly <bjk44@cornell.edu>

Date Jan 13, 2017 at 5:15 PM

Francis

[redacted]

barany@med.cornell.edu

[redacted]

Cornell Illumina Case Overview Figures…

Subject Re: Privileged and Confidential: Followup to January 13th phone meeting, Part 3

From Francis Barany <barany@med.cornell.edu>

To: Pearson, Matthew <mpearson@AKINGUMP.com>, Valerie Cross <vlc1@cornell.edu>

Cc: Weil, Jason <jweil@akingump.com>, Monib Zirvi <matzirvi@yahoo.com>, Goldman Mike <Michael.Goldman@leclairryan.com>, Brian Kelly <bjk44@cornell.edu>

Date Jan 13, 2017 at 5:15 PM

Francis

[redacted]
barany@med.cornell.edu

[redacted]

Cornell Illumina Case Overview Figures…

Subject Re: Privileged and Confidential: Followup to January 13th phone meeting, Part 4

From Francis Barany <barany@med.cornell.edu>

To: Pearson, Matthew <mpearson@AKINGUMP.com>, Valerie Cross <vlc1@cornell.edu>

Cc: Weil, Jason <jweil@akingump.com>, Monib Zirvi <matzirvi@yahoo.com>, Goldman Mike <Michael.Goldman@leclairryan.com>, Brian Kelly <bjk44@cornell.edu>

Date Jan 13, 2017 at 5:16 PM

This and the next email contain a comparison of Illumina products from their "2014 chart" and their 2015 website of products, and also highlights which patents infringe, and arrows to the relevant claims, some slides overlap with previous deck.

Best,

Francis

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

Illumina Chart Figures_01_13_2017_v0…

Illumina Chart Figures_01_13_2017_v0…

Subject Re: Privileged and Confidential: Followup to January 13th phone meeting, Part 5

From Francis Barany <barany@med.cornell.edu>

To: Pearson, Matthew <mpearson@AKINGUMP.com>, Valerie Cross <vlc1@cornell.edu>

Cc: Weil, Jason <jweil@akingump.com>, Monib Zirvi <matzirvi@yahoo.com>, Goldman Mike <Michael.Goldman@leclairryan.com>, Brian Kelly <bjk44@cornell.edu>

Date Jan 13, 2017 at 5:18 PM

5 emails with 6 attachments total sent, kindly confirm receipt.

See you Tuesday!

Francis

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

Illumina Chart Figures_01_13_2017_v0…

Subject Privileged and confidential: papers and patents, part 1A

From Francis Barany <barany@med.cornell.edu>

To: Pearson, Matthew <mpearson@akingump.com>, Valerie Cross <vlc1@cornell.edu>

Cc: Monib Zirvi <matzirvi@yahoo.com>, Francis Barany <barany@med.cornell.edu>

Date Jan 19, 2017 at 9:13 AM

1. Original papers of the first publications of PCR, Taqman, OLA, LCR, LDR, SDA, 3SR — the classic papers of the field. These show that only Ulf Landegren and myself used the style of primers as rectangular bars, with curved or angled regions when not matched to template. Further, only I used the patterns on the bars with different sections filled with different stripes or cross-hatches, exactly what Illumina copied in their hand-drawings.

Francis

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

3SR_Gingeras_PNAS-1990.pdf

Chehab PNAS 1989.pdf

Cloning_PCR_Erilich_Science_1986.pdf

Exponential amplification of nucleic acid…

Genetic_Disease_Detection_LCR_LDR…

Subject Privileged and confidential: papers and patents, part 1B

From Francis Barany <barany@med.cornell.edu>

To: Pearson, Matthew <mpearson@akingump.com>, Valerie Cross <vlc1@cornell.edu>

Cc: Monib Zirvi <matzirvi@yahoo.com>, Francis Barany <barany@med.cornell.edu>

Date Jan 19, 2017 at 9:15 AM

Francis

[redacted]

barany@med.cornell.edu

[redacted]

LCR_in_PCR_World_Barany_1991.pdf

LCR_review2_Barany_Batt-1994.pdf

Nickerson_Hood_PCR_OLA_PNAS_19…

OLA_Landegren_Science_1988.pdf

PCR_review_Gelfand_Science_1991.pdf

Subject Privileged and confidential: papers and patents, part 2

From Francis Barany <barany@med.cornell.edu>

To: Pearson, Matthew <mpearson@akingump.com>, Valerie Cross <vlc1@cornell.edu>

Cc: Monib Zirvi <matzirvi@yahoo.com>, Francis Barany <barany@med.cornell.edu>

Date Jan 19, 2017 at 9:15 AM

2. Some reviews on next-generation sequencing technologies — the 10-year retrospective by Dick McCombie has some really nice figures.

Francis

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

Cancer_Exome_Sequencing_Review_2…

Impact next gen sequencing review 200…

Low_abundant_mutation_seq_review_2…

Next Gen Sequencing review_NB_2008…

Next_Gen_Seq_review_Apr_2009.pdf

Sequencing_applications_review_2012….

Ten_Years_NGS_Technology_2016.pdf

Subject Privileged and confidential: papers and patents, part 1C

From Francis Barany <barany@med.cornell.edu>

To: Pearson, Matthew <mpearson@akingump.com>, Valerie Cross <vlc1@cornell.edu>

Cc: Monib Zirvi <matzirvi@yahoo.com>, Francis Barany <barany@med.cornell.edu>

Date Jan 19, 2017 at 9:15 AM

Francis

[redacted]

barany@med.cornell.edu

[redacted]

PCR_Science_1988.pdf

Quantitative assays based on the use o…

Replicatable RNA reporters_Kramer_19…

SDA_-Walker_PNAS-1992.pdf

Taqman_Gelfand_PNAS-1991.pdf

Subject Privileged and confidential: papers and patents, part 3

From Francis Barany <barany@med.cornell.edu>

To: Pearson, Matthew <mpearson@akingump.com>, Valerie Cross <vlc1@cornell.edu>

Cc: Monib Zirvi <matzirvi@yahoo.com>, Francis Barany <barany@med.cornell.edu>

Date Jan 19, 2017 at 9:15 AM

3. The two patents where Illumina NGS explicitly state that NGS uses “spatially addressable arrays”. I already gave you files of the other patents where Illumina claims sequencing on bead arrays — in the folder called “Illumina Universal bead arrays Filings". It is very important that we establish that Illumina and David Walt only made assembled arrays. We taught them how to make the arrays addressable. We also teach how to use our technology for determining the nucleotide sequence at defined locations on our target.

Kindly confirm you got parts 1A, 1B, 1C, 2, & 3

Francis

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

US7414116_labelled_Nucleotides_Illum…

US8563477_Modified_Molecular_Array…

Subject Privileged and confidential: papers and patents, part 4

From Francis Barany <barany@med.cornell.edu>

To: Pearson, Matthew <mpearson@akingump.com>, Valerie Cross <vlc1@cornell.edu>

Cc: Monib Zirvi <matzirvi@yahoo.com>, Francis Barany <barany@med.cornell.edu>

Date Jan 19, 2017 at 9:28 AM

Dear Matthew,

Yes, here are the tiffs showing the rivets and bead arrays.

We have porous surfaces covered in our specs and claims…

Best,

Francis

[redacted]
barany@med.cornell.edu

[redacted]

Subject Re: Privileged and confidential: papers and patents, part 4

From Monib Zirvi <matzirvi@yahoo.com>

To: Francis Barany <barany@med.cornell.edu>

Cc: Pearson, Matthew <mpearson@akingump.com>, Valerie Cross <vlc1@cornell.edu>

Date Jan 19, 2017 at 10:01 AM

Here is a photo of beads arrays and the rivets:

Sent from my iPhone

On Jan 19, 2017, at 9:28 AM, Francis Barany <barany@med.cornell.edu> wrote:

Dear Matthew,

Yes, here are the tiffs showing the rivets and bead arrays.

We have porous surfaces covered in our specs and claims…

Best,

Francis

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

View less

<Rivets_images.jpeg>

<Beads_on_Array_Electron_Micrograph.tiff>

Subject RE: Privileged and confidential: papers and patents, part 3

From Pearson, Matthew <mpearson@AKINGUMP.com>

To: Francis Barany <barany@med.cornell.edu>, Valerie Cross <vlc1@cornell.edu>

Cc: Monib Zirvi <matzirvi@yahoo.com>

Date Jan 19, 2017 at 10:01 AM

All received

From: Francis Barany [mailto:barany@med.cornell.edu]
Sent: Thursday, January 19, 2017 9:15 AM
To: Pearson, Matthew; Valerie Cross
Cc: Monib Zirvi; Francis Barany
Subject: Privileged and confidential: papers and patents, part 3

3. The two patents where Illumina NGS explicitly state that NGS uses "spatially addressable arrays". I already gave you files of the other patents where Illumina claims sequencing on bead arrays — in the folder called "Illumina Universal bead arrays Filings". It is very important that we establish that Illumina and David Walt only made assembled arrays. We taught them how to make the arrays addressable. We also teach how to use our technology for determining the nucleotide sequence at defined locations on our target.

Kindly confirm you got parts 1A, 1B, 1C, 2, & 3

Francis

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

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The information contained in this e-mail message is intended only for the personal and confidential use of the recipient(s) named above. If you have received this communication in error, please notify us immediately by e-mail, and delete the original message.

Subject Re: Privileged and confidential: papers and patents, part 4

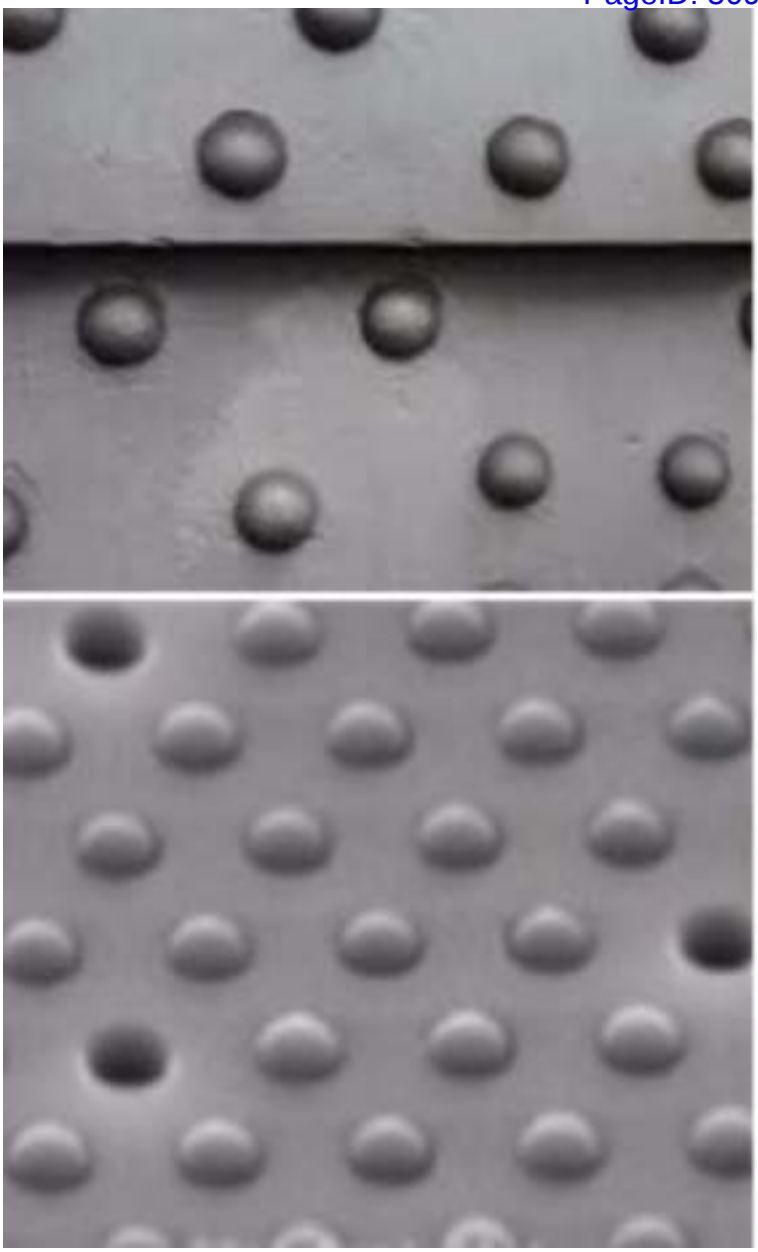
From Monib Zirvi <matzirvi@yahoo.com>

To: Francis Barany <barany@med.cornell.edu>

Cc: Pearson, Matthew <mpearson@akingump.com>, Valerie Cross <vlc1@cornell.edu>

Date Jan 19, 2017 at 10:38 AM

A better version



Sent from my iPhone

On Jan 19, 2017, at 10:01 AM, Monib Zirvi
<matzirvi@yahoo.com> wrote:

Here is a photo of beads arrays and the rivets:

<image1.png>

View more

Subject Re: Privileged and confidential: papers and patents, part 3

From Francis Barany <barany@med.cornell.edu>

To: Pearson, Matthew <mpearson@AKINGUMP.com>

Cc: Valerie Cross <vlc1@cornell.edu>, Monib Zirvi <matzirvi@yahoo.com>

Date Jan 19, 2017 at 4:41 PM

Dear Matthew,

Kindly see enclosed paper just published titled: Targeted DNA sequencing and in situ mutation analysis using mobile phone microscopy.

This is based off the work of Lizardi (original paper and patent also enclosed, filed in 1998, years after our filing).

They are using a ligation reaction and to this day are calling it targeted sequencing — built on our original work of PCR-LDR and PCR-PCR-LDR for sequencing.

I hope this helps.

Best,

Francis

[redacted]
barany@med.cornell.edu

[redacted]

> On Jan 19, 2017, at 10:01 AM, Pearson, Matthew <mpearson@AKINGUMP.com> wrote:

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All received

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Kindly confirm you got parts 1A, 1B, 1C, 2, & 3

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[redacted]
barany@med.cornell.edu

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Targeted DNA sequencing and in situ m…

Mutation_detection_single_molecule_c…

US6316229_Lizardi.pdf

Subject Privileged and Confidential: Zipcode in software (Cornell and Akin Gump only)

From Francis Barany <barany@med.cornell.edu>

To: Pearson, Matthew <mpearson@akingump.com>, Valerie Cross <vlc1@cornell.edu>

Cc: Monib Zirvi <matzirvi@yahoo.com>, Francis Barany <barany@med.cornell.edu>

Date Feb 18, 2017 at 11:36 PM

Dear Matthew and Valerie,

Monib and I were reviewing the “Dynamically Linked Library" (dll) for DMAP files that are used for all of Illumina’s beadchips. Monib was able to download the software from the Illumina site. There are two dll files. One is called “Common Verascan.dll”, and the other is called “Illumina datafiles.dll”. These files are used to decode all the beadchips including infinitum chips, methylation chips (which also use the infinium approach) as well as the "Sentrix Universal Array Matrix” (which are straight zipcode arrays used for analyzing miRNA).

Monib was able to decompile the two files, and found data structures that used the word “zipcode" multiple times, however, this is hidden and not seen by the user — kindly see enclosed pdf of 5 slides. If the source codes for these two dll files was not turned over to Akin Gump during discovery, that is a deliberate omission.

Questions:

1. Did Illumina reveal this information to Akin Gump in the discovery process for the word “zipcode”?

2. If they did not reveal this information is this

grounds for a mistrial, in terms of willful concealment of material facts? The reason this is important is because Illumina claims their arrays — including the

because Illumina claims their arrays — including the infinium arrays — are not “zipcode” arrays.

3. If 2 is correct, should Judge Stark be notified of this right away before any further decisions are made (i.e. on the summary judgement)?

4. Can we use this to open up grounds for re-argument (e.g. for the claim language concerning what constitutes a capture oligonucleotide probe)?

Thanking you again for all your help,

Best,

Francis & Monib

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

Cornell Illumina Case Array Figures_02…

Subject Re: Privileged and Confidential: Zipcode in software (Cornell and Akin Gump only)

From Monib Zirvi <matzirvi@yahoo.com>

To: Francis Barany <barany@med.cornell.edu>

Cc: Pearson, Matthew <mpearson@akingump.com>, Valerie Cross <vlc1@cornell.edu>

Date Feb 19, 2017 at 12:47 AM

●●●○○ Verizon 12:47 AM 33%
injury.findlaw.com

Things to Remember About Discovery

- Keep in mind that it is very likely that anything and everything will come out at some point in the discovery process.
- It is imperative that you be honest with your attorney about the facts and documents that may come out. He or she can't do the best job if you don't disclose everything.
- Discovery can be lengthy, expensive, intrusive, and frustrating. Whether you want to have your life opened to that kind of scrutiny should play a role in your decision whether or not to start a lawsuit.
- Be honest. Nothing will make you lose a case quicker than lying in discovery and getting caught, and it is likely that you will get caught if you are purposefully dishonest.

Don't Go It Alone: Talk to an Attorney for Free

The discovery process should never be taken lightly. Opposing counsel will do everything it can to challenge your story, poke holes in your narrative, or even discredit your character -- whatever it takes to win the case. So shouldn't you also have representation at your side when being deposed or asking for documents? Get a free claim evaluation to learn more about the merits of your case.

Email 19 Share 6984 Tweet 7
Share 69

Sent from my iPhone

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[redacted]
barany@med.cornell.edu

[redacted]

<Cornell Illumina Case Array
Figures_02_18_2017_v04_p195-199.pdf>

Figures_02_16_2017_v04_p193-199.pdf>

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Subject Re: Privileged and Confidential: Zipcode in software (Cornell and Akin Gump only)

From Valerie Cross Dorn <vlc1@cornell.edu>

To: Francis Barany <barany@med.cornell.edu>, Monib Zirvi <matzirvi@yahoo.com>

Cc: Matt Pearson <mpearson@akingump.com>

Date Feb 20, 2017 at 7:25 PM

Francis and Monib,

I touched base with Matt to ask him not to respond directly to your email. I want to make sure you understand that your questions about the lawsuit and litigation tactics should be directed to me and I will work to get answers from appropriate sources, including Matt.

As you know, we don't have the exclusive right to use the term "zipcode" and as you also know, the legal briefs we filed made arguments that were available to us based on facts the discovery record. A mistrial is not available, but we did file a motion for a discovery sanction related to DMAP files. That issue provides no grounds to re-open the claim construction process. I will confer with our outside counsel to see if there is additional information that can be shared with you.

Valerie

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>
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>
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[redacted]

<Cornell Illumina Case Array
Figures_02_18_2017_v04_p195-199.pdf>

View less

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From Francis Barany <barany@med.cornell.edu>

To: Valerie Cross <vlc1@cornell.edu>

Cc: Monib Zirvi <matzirvi@yahoo.com>, Matt Pearson <mpearson@akingump.com>, Francis Barany <barany@med.cornell.edu>

Date Feb 20, 2017 at 10:39 PM

Dear Valerie,

Thank you so much for getting back to us on a holiday weekend. Seeing your answer, we realized we were communicating in "science speak" and that you did not understand what we were trying to articulate, so we will try to make this clear in common language. For example, we fully recognize that the US postal service coined the term "zip code". However, we were the ones who used the term to describe encoding and decoding DNA sequences – in short this is the "operating system" we developed. Perhaps the following definitions will help clarify it for you (forgive me if this is already crystal clear for you, if not please call me ASAP):

Zip code (Universal) Addressable Array = Cell phone

LDR-PCR, PCR-LDR, PCR-PCR-LDR, all used with zip code addressable array are like Apps on your cell phone.

- LDR-PCR is like a Facebook App search to find everyone who went to your high school.
- PCR-LDR, is like a Google App search to find where your 5 best friends from your childhood live today.
- PCR-PCR-LDR is like a LinkedIn App search to find all Pediatricians in Delaware.

Types of Arrays:

- Zip code (Universal) Addressable Array = Cell phone.
- Pure Hybridization Array = Yellowpages book.
- Random beads assembled on solid support = All pages from phone book, randomly assembled.
- Zip code coupled to target sequences; Addressable Arrays = Google search of Yellowpages.com.

Types of Primers & Probes:

- Zip code = Google search word. (i.e. Oil)
- Target sequence = Specific Website. (www.foodnetwork.com)
- Zip code coupled to Zip code = Two Google search words linked together. (i.e. olive oil, vegetable oil, or garden vegetable)
- Zip code coupled to Target sequence = Google search word linked to a Specific Website. (i.e. “olive” links to “Olive Garden Italian Restaurant” www.olivegarden.com).

(All of the above primers and probes are fully described in the ‘917 and ‘470 series patents.)

As you know, Illumina does not make addressable arrays. They make assembled arrays. The beads go into random places, and if you use an assembled array “as is” to try to identify SNPs or look at expression data, you will see a bunch of random red or green fluorescent spots, and it is impossible to interpret.

To interpret the data, one needs addressable arrays. There are two ways to make addressable arrays – you can put your zipcode oligos down at known locations in an X-Y coordinate, or you can use zipcodes to decode where randomly distributed oligos (i.e. on beads) have been placed, again in an X-

dimension and in a Y-dimension. When using the second approach, one then needs a “cheat sheet” for each array you make, that tells you which bead is in which well, by giving the X coordinate and the Y coordinate (called the BeadMap). That is the DMAP file you refer to in your email.

This was the key moment in the Zebala case, when David Walt admitted that to decode the arrays you just needed to know two dimensions, the X-dimension and the Y-dimension (see enclosed revised deck). You will also notice part 5, the red box at the bottom that says “Name: string zipcode”, and then beneath that “Xvalues” and “Yvalues”.

It is mission critical for us to see the original programing code, also known as the “source code” for the original dll files, for example in SQL, or C++, or Microsoft.net, or Java, or JavaScript, or other programing langauges. That is different from the files Monib downloaded, or the DMAP files that are made for each separate Beadchip. By way of example, in our own patent listing about 4,000 zipcodes (initially published as WO2001079548), we wrote a program to make sure there wouldn’t be cross-hybridization problems between a zipcode the sequence at the junction of another zipcode and target sequence (i.e. the composite oligo) – this was several hundred lines of code and took up 13 pages in a printout (enclosed, Fig. 35). As you can see, the original program often has comments that explain what is being done in the program.

Likewise, we strongly suspect – given that the compiled listing already links the words

“zipcode” with “Xvalues” and “Yvalues” that the source code would clearly delineates exactly what is going on in the program.

The key reason this is important is because Illumina claims their arrays — including the infinium SNP & copynumber

their arrays — including the Infinium CNV & copynumber BeadChip, infinium methylation BeadChip, and expression BeadChip arrays — are not “zipcode” arrays.

We all know this is not true. WE believe a compelling argument can be made that Illumina’s failure to release the original source code for the “Common Verascan.dll”, and “Illumina datafiles.dll” files (and additional programs as detailed below) was to HIDE their own admission that all their arrays are really zipcode arrays, and this constitutes willful concealment of material facts.

Now it is time for Judge Stark to know in no uncertain terms that Illumina has mislead him, that the Illumina Infinium BeadChips and all other Illumina array products are all zipcode arrays.

Furthermore…

We only recently uncovered that in Illumina’s initial submition of provisional application 60/227,948 (M. Chee and K. Gunderson) on August 25, 2000, they called our zip codes as “IllumaCodes”. In Illumina’s full application 09/940,185 filed on August 27, 2001 (K. Gunderson & M. Chee), they renamed them as “Seq. ID No.”, and further, only provided the sequence information as scanned tables. The USPTO wrote a letter to Illumina on October 19, 2001 stating that applicants must provide an initial computer readable form (CRF) copy. Illumina obviously tried to limit the USPTO’s ability to search the sequences, despite the fact they were clearly generated on a computer.

Since the GoldenGate assay, and other Illumina publication refer to our zip codes as “IllumiCode” (trademarked) array, and the individual addresses as “illumiCodes” (i.e. illumiCode # 561, #217, #1024), it would not be unreasonable to hypothesize that there is some overlap between the list of “IllumaCodes” and “illumiCodes”. (Put another way, the probability of randomly choosing two names where 9 of 10 letters match in order is 26 to the 9th power, which is 1 in 5.4 trillion, or to put it in DNA language, there would be substantial cross-hybridization!).

Adding to this, in the First Amendment to the Joint

Development Agreement, signed by John R. Stuelpnagel and dated March 27, 2001 (in other words before the August 27, 2001 submission), there is a call for defining and developing "Tag Sequences for the Collaboration Product", which we all now know are just another name for zipcode sequences.

All such sequences are covered by the '917 family of patents. This leads us to the following questions:

1. Did Illumina provide the source codes for the "Common Verascan.dll", and "Illumina datafiles.dll" files – both of which contain the word "zipcode" -- to Akin Gump?

2. Did Illumina provide the source codes for the software they wrote to generate the initial "IllumaCodes", and all subsequent revisions to Akin Gump? Do these programs contain the word "zipcode"?

3. Did the source codes for the software they wrote to generate the initial "IllumaCodes" contain the initial 16 zipcodes from Barany's original unpublished 465 list, or did they add them afterwards to the tables in their US20030096239 patent application?

4. Did the source codes for the software they wrote to generate the initial "IllumaCodes" contain a subroutine to check a new sequence against all previous sequences for complementarity scores of < 18 (less than 18), or did the source code use the term "<= 18" (less than or equal to, which is what Barany taught, and there is one such match among the IllumaCodes)?

5. Did Illumina provide the source codes for the "Tag Sequences for the Collaboration Product", and all subsequent revisions to Akin Gump? Do these programs contain the word

"zipcode"?

6. Did Illumina provide the source codes for the software they wrote to generate the current set of "IllumiCodes" or whatever they are calling the zipcodes on their current "Illumina infinium humanmethylation450 beadchip" "llumina Infinium HD BeadChip", "Sentrix Universal Array Matrix", "Illumina Human Whole-Genome DASL HT Assay", "HumanHT-12 v4 Expression BeadChip", or any other arrays sold by Illumina, and all subsequent revisions to Akin Gump? Do these programs contain the word "zipcode"?

7. Do you know which of Illumina's current and prior BeadChip

products use our original 16 zip codes? The 60/172,106 application as originally filed on Dec. 23, 1999? The 60/180810 provisional application, Filed Feb. 7, 2000, that refers to universal BeadArrays with 128 unique addresses (zipcodes)?

If Illumina did not reveal the source code, i.e. original programing code, can we force them in court with a motion, such that we reveal their willful concealment of material facts?

Would this be grounds for appeal, if the source code was never revealed to Judge Stark and the Cornell legal team?

If Illumina did reveal the source code information, can we inform Judge Stark that Illumina themselves refer to the addresses on said arrays as “zipcodes” contradicting their prior assertion that these are not zipcode arrays?

We would like to have a webex meeting on Friday, February 24th with Matthew and Valerie (if you are available) to discuss these issues. As the inventors, we appreciate that you take our concerns seriously, and the time you are spending to explain the legal issues to us.

Would you kindly let us know what potential time slots would work for you on Friday, February 24th?

Most appreciated,

Francis & Monib

[redacted]

[redacted]

barany@med.cornell.edu

[redacted]

P.S. We understand the concept of the protective order to keep secret from the inventors confidential Illumina information. However, since WE were the ones who originally designed those 16 zipcode sequences (and we have numerous ways of proving it could not have been designed by Illumina), in our view these sequences belong to us and cannot be considered "Illumina confidential information". Therefore, they should NOT be covered by the protective order, and we should know the answers to point 7 above.

> On Feb 20, 2017, at 7:24 PM, Valerie Cross Dorn <vlc1@cornell.edu> wrote:
>
> Francis and Monib,
>
> I touched base with Matt to ask him not to respond directly to your email. I want to make sure you understand that your questions about the lawsuit and litigation tactics should be directed to me and I will work to get answers from appropriate sources, including Matt.
>
> As you know, we don't have the exclusive right to use the term "zipcode" and as you also know, the legal briefs we filed made arguments that were available to us based on facts the discovery record. A mistrial is not available, but we did file a motion for a discovery sanction related to DMAP files. That issue provides no grounds to re-open the claim construction process. I will confer with our outside counsel to see if there is additional information that can be shared with you.
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> Valerie

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Cornell Illumina Case Array Figures_02…

WO2001079548-PAMPH-711_Gerry_Zi…

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To: Francis Barany <barany@med.cornell.edu>

Cc: Valerie Cross <vlc1@cornell.edu>, Matt Pearson <mpearson@akingump.com>

Date Feb 20, 2017 at 11:09 PM

Dear Valerie,

I agree. If a motion can be submitted to Judge Stark to force Illumina to reveal the original source code for CommonVeraScan.dll and Illuminadatafiles.dll (which are used to read X and Y locations of each Zipcode in DMAP files for BeadChips), it will be abundantly clear that they are ZipCode Arrays, thus PROVING Cornell's allegations.

Monib

Sent from my iPhone

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- Zip code = Google search word. (i.e. Oil)
- Target sequence = Specific Website. (www.foodnetwork.com)
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All such sequences are covered by the ‘917 family of patents. This leads us to the following questions:

1. Did Illumina provide the source codes for the “Common Verascan.dll”, and “Illumina datafiles.dll” files – both of which contain the word “zipcode” -- to Akin Gump?

2. Did Illumina provide the source codes for the software they wrote to generate the initial “IllumaCodes”, and all subsequent revisions to Akin Gump? Do these programs contain the word “zipcode”?

3. Did the source codes for the software they wrote to generate the initial “IllumaCodes” contain the initial 16 zipcodes from Barany’s original unpublished 465 list, or did they add them afterwards to the tables in their US20030096239 patent application?

4. Did the source codes for the software they wrote to generate the initial “IllumaCodes” contain a subroutine to check a new sequence against all previous sequences for complementarity scores of < 18 (less than 18), or did the source code use the term “<= 18” (less than or equal to, which is what Barany taught, and there is one such match among the IllumaCodes)?

5. Did Illumina provide the source codes for the “Tag

Sequences for the Collaboration Product", and all subsequent revisions to Akin Gump? Do these programs contain the word "zipcode"?

6. Did Illumina provide the source codes for the software they wrote to generate the current set of "IllumiCodes" or whatever they are calling the zipcodes on their current "Illumina infinium humanmethylation450 beadchip" "llumina Infinium HD BeadChip", "Sentrix Universal Array Matrix", "Illumina Human Whole-Genome DASL HT Assay", "HumanHT-12 v4 Expression BeadChip", or any other arrays sold by Illumina, and all subsequent revisions to Akin Gump? Do these programs contain the word "zipcode"?

7. Do you know which of Illumina's current and prior BeadChip products use our original 16 zip codes? The 60/172,106 application as originally filed on Dec. 23, 1999? The 60/180810 provisional application, Filed Feb. 7, 2000, that refers to universal BeadArrays with 128 unique addresses (zipcodes)?

If Illumina did not reveal the source code, i.e. original programing code, can we force them in court with a motion, such that we reveal their willful concealment of material facts?

Would this be grounds for appeal, if the source code was never revealed to Judge Stark and the Cornell legal team?

If Illumina did reveal the source code information, can we inform Judge Stark that Illumina themselves refer to the addresses on said arrays as "zipcodes" contradicting their prior assertion that these are not zipcode arrays?

We would like to have a webex meeting on Friday, February 24th with Matthew and Valerie (if you are available) to discuss these issues. As the inventors, we appreciate that you take our concerns seriously, and the time you are spending to explain the legal issues to us.

Would you kindly let us know what potential time slots would work for you on Friday, February 24th?

Most appreciated,

Francis & Monib

[redacted]

[redacted]

barany@med.cornell.edu

[redacted]

P.S. We understand the concept of the protective order to keep secret from the inventors confidential Illumina information. However, since WE were the ones who originally designed those 16 zipcode sequences (and we have numerous ways of proving it could not have been designed by Illumina), in our view these sequences belong to us and cannot be considered "Illumina confidential information". Therefore, they should NOT be covered by the protective order, and we should know the answers to point 7 above.

> On Feb 20, 2017, at 7:24 PM, Valerie Cross Dorn <vlc1@cornell.edu> wrote:
>
> Francis and Monib,
>
> I touched base with Matt to ask him not to respond directly to your email. I want to make sure you understand that your questions about the lawsuit and litigation tactics should be directed to me and I will work to get answers from appropriate sources, including Matt.
>
> As you know, we don't have the exclusive right to use the term "zipcode" and as you also know, the legal briefs we filed made arguments that were available to us based on facts the discovery record. A mistrial is not available, but we did file a motion for a discovery sanction related to DMAP

files. That issue provides no grounds to re-open the claim construction process. I will confer with our outside counsel to see if there is additional information that can be shared with you.

Valerie

<Cornell Illumina Case Array Figures_02_18_2017_v04_p197-203.pdf>
<WO2001079548-PAMPH-711_Gerry_Zirvi_Barany_2001_Fig35.pdf>
<GoldenGate_Assay_Illumina_slide3.tiff>

View less

Subject Privileged and Confidential: Control addresses may be another opportunity 2

From Francis Barany <barany@med.cornell.edu>

To: Valerie Cross <vlc1@cornell.edu>, Pearson, Matthew <mpearson@AKINGUMP.com>

Cc: matzirvi@yahoo.com <matzirvi@yahoo.com>, Francis Barany <barany@med.cornell.edu>

Date Feb 21, 2017 at 12:53 PM

Francis

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

microrna_assay_guide_11317302_reva…

Subject Privileged and Confidential: Control addresses may be another opportunity 1

From Francis Barany <barany@med.cornell.edu>

To: Valerie Cross <vlc1@cornell.edu>, Pearson, Matthew <mpearson@AKINGUMP.com>

Cc: Monib Zirvi <matzirvi@yahoo.com>, Francis Barany <barany@med.cornell.edu>

Date Feb 21, 2017 at 12:53 PM

Dear Valerie and Matthew,

You both understand that our original '470 series patents cover PCR primers comprising of composite zipcodes, a first zipcode covalently linked to a second zipcode, and such primers are used for PCR amplifying primary LDR or PCR products (Figures 13 & 18). When such composite zipcode primers hybridize to the universal array, the absence of signal indicates a particular SNP or allele is missing, however, there is no target sequence hybridized to the universal array. This shows that the Judge Stark was misled by Illumina's false argument that "In fact, the Array Patents contain no disclosure of any embodiment in which the oligonucleotide contacted to the array does not contain a target-specific portion".

However, we may have overlooked another potential opportunity to cover the infinium BeadChips, Infinium HD Methylation BeadChips, and Whole-Genome Direct Expression BeadChips on the existing claims as written.

All chips require control oligos. Our patents cover zipcode arrays where the addresses are greater than 16 bases and artificial sequences.

We realized that the control addresses within the infinium and other beadchips should cover such zipcode sequences. Such addresses cannot be

zipcode sequences. Such addresses cannot be claimed by Illumina as “hybridization array” addresses, since they do NOT contain target DNA.

Enclosed in this and the followup emails are the appropriate manuals and the pages wherein such addresses are listed.

1. infinium-assay-lab-setup-and-procedures-11322460-01.pdf
Please see pages 28-33.

Controls on Page 28 & 29 list the Bead Type ID#. At the bottom of page 28 are 20 hybridization controls, top of page 29 are 10 more hybridization controls, for a total of 30 probes. These are sample independent controls that hybridize to synthetic targets that are added (see diagram on page 32). There are also
sample dependent stringency controls, which appear to hybridize to the zip-code region (see diagram on bottom of page 32).

2. Infinium_hd_meth_assay_ug_15019519_revb.pdf
Please see pages 236-244.

Now, they no longer list bead type ID#. They just give a number on the array, see pages 236-237. They mention hybridization controls on page 239, but now the diagram is missing.
They mention specificity controls, but no stringency controls.

3. wggex_direct_hybridization_assay_guide_11322355_a.pdf
HumanHT-12_V4_0_R2_15002873_B_small.xlsx (I deleted most of the human sequences so the file would be small enough to send you)
Please see pages 77-81of pdf.

You will notice there are Ambion ERCC RNA spike-in controls. You will see these listed in the xlsx file. Also, page 81, figure 58 gives a negative control diagram. They state:

"This category consists of probes of random sequence selected to have no corresponding targets in the genomes. The mean signal of these probes defines the system background. This is a comprehensive measurement of background, representing the imaging system background as well as any signal resulting from non-specific binding of dye or cross-hybridization. The GenomeStudio application uses the signals and signal standard deviation of these probes to establish gene expression detection limits."

We could state the random sequences could also be used as a zipcode sequences, and since there is hybridization to these positions, they qualify as non-target sequences. Further, to identify the position of those artificial sequences, they still needed to give them zipcode ID numbers, as shown on the excel file.

4. microrna_assay_guide_11317302_reva.pdf
Please see pages 147-157.

These are straight zipcode arrays (Sentrix Universal Array Matrix).
Illumicode Control sequences are listed on pages 148-150.

Hope this helps, and Matthew, please confirm your availability to speak directly with us and Valerie on Friday.

Best,

Francis & Monib

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

infinium-assay-lab-setup-and-procedure…

Infinium_hd_meth_assay_ug_1501951…

wggex_direct_hybridization_assay_guid…

HumanHT-12_V4_0_R2_15002873_B_…

Subject RE: Illumina-Cornell - Cross-Dorn - Kelly

From Roger.Chin@lw.com <Roger.Chin@lw.com>

To: <barany@med.cornell.edu>, <matzirvi@yahoo.com>

Cc: <vlc1@cornell.edu>, <mpearson@akingump.com>, <Doug.Lumish@lw.com>

Date Feb 22, 2017 at 9:19 PM

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Frances,

Matt and I were able to connect and discuss the recent legal analysis as well as the issues you raised with him about control beads. Both of us are available to follow up on those points on Friday at 11 am Eastern. Since we will have a few slides to help organize the discussion, I will send around a separate web meeting invitation for that time that will allow us to present those slides.

Regards,
Roger

Roger J. Chin

LATHAM & WATKINS LLP

[redacted]

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order to protect our business and verify compliance with our policies and relevant legal requirements.

Subject Illumina-Cornell - Cross-Dorn - Kelly (Latham Hosted)

From Roger.Chin@lw.com <Roger.Chin@lw.com>

To: <barany@med.cornell.edu>, <matzirvi@yahoo.com>, <vlc1@cornell.edu>, <Rip.Finst@thermofisher.com>, <sean.boyle@thermofisher.com>, <bjk44@cornell.edu>, <Doug.Lumish@lw.com>, <mpearson@AKINGUMP.com>

Date Feb 22, 2017 at 9:21 PM

Audio Dial-In Information:

United States (Toll Free): [redacted]

ACCESS CODE: [redacted]

Web Meeting Information:

Web Meeting URL

https://www.connectmeeting.att.com

Meeting Number: [redacted]

Access Code: [redacted]

Personalized Web Meeting URL

(Automatically enters Meeting Number and Access Code.)

[redacted]

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policies and relevant legal requirements.

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---

untitled.ics

Subject RE: (Forward to others) WebEx meeting invitation: Illumina-Cornell - Cross-Dorn - Kelly

From Roger.Chin@lw.com <Roger.Chin@lw.com>

To: <mpearson@AKINGUMP.com>, <barany@med.cornell.edu>, <matzirvi@yahoo.com>, <vlc1@cornell.edu>, <Rip.Finst@thermofisher.com>, <sean.boyle@thermofisher.com>, <bjk44@cornell.edu>, <Doug.Lumish@lw.com>

Date Feb 22, 2017 at 9:21 PM

Since Matt and I will have a few slides that we would like to discuss, can we plan to use our dial-in/log-in instead? The new information is attached and below, and I will also send it separately as an Outlook invitation.

Audio Dial-In Information:
United States (Toll Free): [redacted]
ACCESS CODE: [redacted]

Web Meeting Information:
Web Meeting URL
https://www.connectmeeting.att.com
Meeting Number: [redacted]
Access Code: [redacted]
Personalized Web Meeting URL
(Automatically enters Meeting Number and Access Code.)
[redacted]
For first use, follow the prompts for the software download.

Regards,
Roger

Roger J. Chin

LATHAM & WATKINS LLP
[redacted]

From: Francis Barany <messenger@webex.com>
Subject: (Forward to others) WebEx meeting invitation: Illumina-Cornell - Cross-Dorn - Kelly
Date: February 22, 2017 at 4:21:08 PM EST
To: <barany@med.cornell.edu>
Reply-To: <barany@med.cornell.edu>

You can forward this invitation to others.

Hello,

Francis Barany invites you to join this WebEx meeting.

Illumina-Cornell - Cross-Dorn - Kelly
Friday, February 24, 2017
11:00 am | Eastern Standard Time (New York, GMT-05:00) | 1 hr
Meeting number (access code): [redacted]
Meeting password: [redacted]

Add to Calendar

When it's time, join the meeting.

Join by phone
[redacted] Call-in toll number (US/Canada)
Global call-in numbers

Can't join the meeting?

IMPORTANT NOTICE: Please note that this WebEx service allows audio and other information sent during the session to be recorded, which may be discoverable in a legal matter. By joining this session, you automatically consent to such recordings. If you do not consent to being recorded, discuss your concerns with the host or do not join the session.

<WebEx_Meeting.ics>

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Personalized Web Meeting URL

(Automatically enters Meeting Number and Access Code.)

[redacted]

[redacted]

For first use, follow the prompts for the software download.

Subject Privileged and Confidential Re: Illumina-Cornell - SOURCE CODE

From Francis Barany <barany@med.cornell.edu>

To: Roger.Chin@lw.com <Roger.Chin@lw.com>, Douglas Lumish (Doug.Lumish@lw.com) <Doug.Lumish@lw.com>

Cc: Monib Zirvi <matzirvi@yahoo.com>, Valerie Cross <vlc1@cornell.edu>, Pearson, Matthew <mpearson@akingump.com>, Francis Barany <barany@med.cornell.edu>

Date Feb 22, 2017 at 10:06 PM

Dear Roger,

Thank you for connecting with Matthew to discuss your recent legal analysis.

The most important issue is highlighted below in an email sent to Valerie (and Matthew), and has to do with whether Illumina provided the SOURCE CODE of a number of programs they wrote, first to generate zip codes, then to make sure that they matched appropriate zip codes and target sequences, and then to identify the X-Y coordinates of the zipcodes.

I am also enclosing a small pdf that explains the issues about finding the word “zipcode” within the files. The key reason this is important is because Illumina claims their arrays — including the infinium SNP & copy-number BeadChip, infinium methylation BeadChip, and expression BeadChip arrays — are not “zipcode” arrays.

We all know this is not true. WE believe a compelling argument can be made that Illumina’s failure to release the original source code for the “Common Verascan.dll”, and “Illumina datafiles.dll” files (and additional programs as detailed below) was to HIDE their own admission that all

their arrays are really zipcode arrays, and this constitutes willful concealment of material facts.

Looking forward to your slide deck, and talking on Friday @ 11:00 AM Eastern.

With best wishes,

Francis

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

— — — — — — — — — — —

Dear Valerie,

Thank you so much for getting back to us on a holiday weekend. Seeing your answer, we realized we were communicating in "science speak" and that you did not understand what we were trying to articulate, so we will try to make this clear in common language. For example, we fully recognize that the US postal service coined the term "zip code". However, we were the ones who used the term to describe encoding and decoding DNA sequences – in short this is the "operating system" we developed. Perhaps the following definitions will help clarify it for you (forgive me if this is already crystal clear for you, if not please call me ASAP):

Zip code (Universal) Addressable Array = Cell phone

LDR-PCR, PCR-LDR, PCR-PCR-LDR, all used with zip code addressable array are like Apps on your cell phone.

- LDR-PCR is like a Facebook App search to find everyone who went to your high school.
- PCR-LDR, is like a Google App search to find where your 5 best friends from your childhood live today.
- PCR-PCR-LDR is like a LinkedIn App search to find all Pediatricians in Delaware.

Types of Arrays:

- Zip code (Universal) Addressable Array = Cell phone.
- Pure Hybridization Array = Yellowpages book.
- Random beads assembled on solid support = All pages from phone book, randomly assembled.

- Zip code coupled to target sequences; Addressable Arrays = Google search of Yellowpages.com.

Types of Primers & Probes:

- Zip code = Google search word. (i.e. Oil)
- Target sequence = Specific Website. (www.foodnetwork.com)
- Zip code coupled to Zip code = Two Google search words linked together. (i.e. olive oil, vegetable oil, or garden vegetable)
- Zip code coupled to Target sequence = Google search word linked to a Specific Website. (i.e. "olive" links to "Olive Garden Italian Restaurant" www.olivegarden.com).

(All of the above primers and probes are fully described in the '917 and '470 series patents.)

As you know, Illumina does not make addressable arrays. They make assembled arrays. The beads go into random places, and if you use an assembled array "as is" to try to identify SNPs or look at expression data, you will see a bunch of random red or green fluorescent spots, and it is impossible to interpret.

To interpret the data, one needs addressable arrays. There are two ways to make addressable arrays – you can put your zipcode oligos down at known locations in an X-Y coordinate, or you can use zipcodes to decode where randomly distributed oligos (i.e. on beads) have been placed, again in an X-dimension and in a Y-dimension. When using the second approach, one then needs a "cheat sheet" for each array you make, that tells you which bead is in which well, by giving the X coordinate and the Y coordinate (called the BeadMap). That is the DMAP file you refer to in your email.

This was the key moment in the Zebala case, when David Walt admitted that to decode the arrays you just needed to know two dimensions, the X-dimension and the Y-dimension (see enclosed revised deck). You will also notice part 5, the red box at the bottom that says "Name: string zipcode", and then beneath that "Xvalues" and "Yvalues".

It is mission critical for us to see the original programing code, also known as the "source code" for the original dll files, for example in SQL, or C++, or Microsoft.net, or Java, or JavaScript, or other programing langauges. That is different from the files Monib downloaded, or the DMAP files that are made for each separate Beadchip. By way of example, in our own patent listing about 4,000 zipcodes (initially published as WO2001079548),

we wrote a program to make sure there wouldn't be cross-hybridization problems between a zipcode the sequence at the junction of another zipcode and target sequence (i.e. the composite oligo) – this was several hundred lines of code and took up 13 pages in a printout (enclosed, Fig. 35). As you can see, the original program often has comments that explain what is being done in the program.

Likewise, we strongly suspect – given that the compiled listing already links the words "zipcode" with "Xvalues" and "Yvalues" that the source code would clearly delineates exactly what is going on in the program.

The key reason this is important is because Illumina claims their arrays — including the infinium SNP & copynumber BeadChip, infinium methylation BeadChip, and expression BeadChip arrays — are not "zipcode" arrays.

We all know this is not true. WE believe a compelling argument can be made that Illumina's failure to release the original source code for the "Common Verascan.dll", and "Illumina datafiles.dll" files (and additional programs as detailed below) was to HIDE their own admission that all their arrays are really zipcode arrays, and this constitutes willful concealment of material facts.

Now it is time for Judge Stark to know in no uncertain terms that Illumina has mislead him, that the Illumina Infinium BeadChips and all other Illumina array products are all zipcode arrays.

Furthermore…

We only recently uncovered that in Illumina's initial submition of provisional application 60/227,948 (M. Chee and K. Gunderson) on

August 25, 2000, they called our zip codes as "IllumaCodes". In Illumina's full application 09/940,185 filed on August 27, 2001 (K. Gunderson & M. Chee), they renamed them as "Seq. ID No.", and further, only provided the sequence information as scanned tables. The USPTO wrote a letter to Illumina on October 19, 2001 stating that applicants must provide an initial computer readable form (CRF) copy. Illumina obviously tried to limit the USPTO's ability to search the sequences, despite the fact they were clearly generated on a computer.

Since the GoldenGate assay, and other Illumina publication refer to our zip codes as "IllumiCode" (trademarked) array, and the individual addresses as "illumiCodes" (i.e. illumiCode # 561, #217,

#1024), it would not be unreasonable to hypothesize that there is some overlap between the list of "IllumaCodes" and "illumiCodes". (Put another way, the probability of randomly choosing two names where 9 of 10 letters match in order is 26 to the 9th power, which is 1 in 5.4 trillion, or to put it in DNA language, there would be substantial cross-hybridization!).

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Most appreciated,

Francis & Monib

[redacted]

[redacted]

barany@med.cornell.edu

[redacted]

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>
> PRIVILEGED & CONFIDENTIAL

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Regards,
Roger

Roger J. Chin

LATHAM & WATKINS LLP
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Cornell Illumina Case Array Figures_02…

Subject RE: Illumina-Cornell - Cross-Dorn - Kelly (Latham Hosted)

From Roger.Chin@lw.com <Roger.Chin@lw.com>

To: <barany@med.cornell.edu>, <matzirvi@yahoo.com>, <vlc1@cornell.edu>, <Rip.Finst@thermofisher.com>, <sean.boyle@thermofisher.com>, <bjk44@cornell.edu>, <Doug.Lumish@lw.com>, <mpearson@AKINGUMP.com>

Date Feb 23, 2017 at 7:43 PM

I have attached a few slides to help frame the follow-up discussion on legal case assessment and impact of the Markman ruling. We will also be prepared to discuss the questions and issues about the case that Francis and Monib recently raised.

Regards,
Roger

-----Original Appointment-----
From: Chin, Roger (SF)
Sent: Wednesday, February 22, 2017 6:21 PM
To: 'Francis Barany'; 'Monib Zirvi'; 'Valerie Cross'; 'Rip.Finst@thermofisher.com'; 'sean.boyle@thermofisher.com'; 'Brian Kelly'; Lumish, Doug (SV); 'Pearson, Matthew'
Subject: Illumina-Cornell - Cross-Dorn - Kelly (Latham Hosted)
When: Friday, February 24, 2017 8:00 AM-9:00 AM (UTC-08:00) Pacific Time (US & Canada).
Where: https://www.connectmeeting.att.com

Audio Dial-In Information:

United States (Toll Free): [redacted]

ACCESS CODE: [redacted]

Web Meeting Information:

Web Meeting URL

https://www.connectmeeting.att.com

Meeting Number: [redacted]

Access Code: [redacted]

Personalized Web Meeting URL

(Automatically enters Meeting Number and Access Code.)

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Cornell presentation (FB-MZ) 2017.02.2…

Cornell presentation 2017.02.24 final.pdf

Subject Re: Illumina-Cornell - Cross-Dorn - Kelly (Latham Hosted)

From Monib Zirvi <matzirvi@yahoo.com>

To: <Roger.Chin@lw.com>

Cc: <barany@med.cornell.edu>, <vlc1@cornell.edu>, <Rip.Finst@thermofisher.com>, <sean.boyle@thermofisher.com>, <bjk44@cornell.edu>, <Doug.Lumish@lw.com>, <mpearson@AKINGUMP.com>

Date Feb 23, 2017 at 9:13 PM

Thanks for the PowerPoint.

Monib

Sent from my iPhone

On Feb 23, 2017, at 7:42 PM, <Roger.Chin@lw.com> <Roger.Chin@lw.com> wrote:

I have attached a few slides to help frame the follow-up discussion on legal case assessment and impact of the Markman ruling. We will also be prepared to discuss the questions and issues about the case that Francis and Monib recently raised.

Regards,
Roger

-----Original Appointment-----
From: Chin, Roger (SF)
Sent: Wednesday, February 22, 2017 6:21 PM
To: 'Francis Barany'; 'Monib Zirvi'; 'Valerie Cross'; 'Rip.Finst@thermofisher.com'; 'sean.boyle@thermofisher.com'; 'Brian Kelly'; Lumish, Doug (SV); 'Pearson, Matthew'
Subject: Illumina-Cornell - Cross-Dorn - Kelly (Latham Hosted)
When: Friday, February 24, 2017 8:00 AM-9:00 AM (UTC-08:00) Pacific Time (US & Canada).
Where: https://www.connectmeeting.att.com

Audio Dial-In Information:

United States (Toll Free): [redacted]

ACCESS CODE: [redacted]

Web Meeting Information:

Web Meeting URL

https://www.connectmeeting.att.com

Meeting Number: [redacted]

Access Code: [redacted]

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Date Feb 23, 2017 at 9:16 PM

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Date Feb 23, 2017 at 9:19 PM

As a contrast Theranos claimed to have machines that would produce lab results from 20-50 microliters of blood. The data was determined to be unreliable and DID not have proper controls. Theranos will soon be bankrupt with multiple lawsuits and no revenue. Controls matter.

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Date Feb 23, 2017 at 9:20 PM

Understood, we can plan to discuss this point tomorrow morning.

Regards,
Roger

From: Monib Zirvi [mailto:matzirvi@yahoo.com]
Sent: Thursday, February 23, 2017 6:19 PM
To: Chin, Roger (SF)
Cc: barany@med.cornell.edu; vlc1@cornell.edu; Rip.Finst@thermofisher.com; sean.boyle@thermofisher.com; bjk44@cornell.edu; Lumish, Doug (SV); mpearson@AKINGUMP.com
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> **Access Code**: [redacted]
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> *(Automatically enters Meeting Number and Access Code.)*
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Subject PCR/LDR/Universal Array Platforms for the Diagnosis of Infectious Disease

From Monib Zirvi <matzirvi@yahoo.com>

To: <barany@med.cornell.edu>, <roger.chin@lw.com>, <mpearson@akingump.com>

Date Feb 24, 2017 at 6:30 AM

In this paper, fiducial oligonucleotides and their complements were used as controls for universal addressable zipcode arrays. Gerry 1999 also used fiducial oligonucleotides as controls. These capture complements without any target sequence and are essential for the proper operation and data analysis of any embodiment described in the patent. Thus capture oligonucleotide probes only need to have an addressable array component.

Monib

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4381875/

Sent from my iPhone

Subject Privileged and Confidential Re: PCR/LDR/Universal Array Platforms

From Francis Barany <barany@med.cornell.edu>

To: roger.chin@lw.com <roger.chin@lw.com>, Pearson, Matthew <mpearson@akingump.com>

Cc: Monib Zirvi <matzirvi@yahoo.com>, Francis Barany <barany@med.cornell.edu>

Date Feb 24, 2017 at 6:58 AM

Dear Roger and Matt,

Roger, thank you for sending the slides yesterday.

Monib is absolutely correct in his comments below, and I have enclosed the Pingle et al 2010 review, (see Fig 2).

Enclosed also is an earlier review from my lab by Favis in 2005, not sure if you have this already.

Figure 2 shows example of using Fiducials and amplicon controls.

Figures 3 & 4 show LDR-PCR as performed by ABI.

Figure 6 shows the way we QC's our arrays.

Table 1 shows some zip-code sequences.

Recognize any of them?

Looking forward to our discussion this morning at 11:00 AM.

Best,

Francis

[redacted]

[redacted] [redacted]
barany@med.cornell.edu

[redacted]

On Feb 24, 2017, at 6:30 AM, Monib Zirvi <matzirvi@yahoo.com> wrote:

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Monib

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4381875/

Sent from my iPhone

View less

Pingle_PCR_LDR_Univ_Array_Review…

Favis_Gerry_Cheng_Barany_2005_cha…

Subject Re: Privileged and Confidential Re: PCR/LDR/Universal Array Platforms

From Monib Zirvi <matzirvi@yahoo.com>

To: Francis Barany <barany@med.cornell.edu>

Cc: roger.chin@lw.com <roger.chin@lw.com>, Pearson, Matthew <mpearson@akingump.com>

Date Feb 24, 2017 at 7:08 AM

One of the known controls described in these passages from '470 when applied to universal addressable zipcode arrays would include fiducial controls that would hybridize to known addresses and those controls DO NOT contain target sequences and are essential for proper operation and interpretation of the array data.

●●●●○ Verizon LTE 7:03 AM 98%
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and the control SOD gene, respectively.

As an alternative to FIG. 8, FIG. 9 shows the LDR/PCR process of the present invention where, in step 3, the extension products are captured on an array of capture oligonucleotide addresses. The capture oligonucleotide probes can be complementary to a nucleotide sequence across the ligation junction. The number of gene copies captured on the array of capture oligonucleotides is then determined by fluorescent quantification as compared with known controls. In FIG. 8, such analysis of the array indicates ligation product sequences hybridizing to gene-specific addresses, where the fluorescent intensity represents amplification of the Her-2 gene, loss of heterozygosity of the p53 gene, and the control SOD gene, respectively.

FIG. 10 is a schematic diagram depicting an LDR/PCR process for multiplex detection of gene amplifications and deletions. Here, the ratio of the Her-2/neu gene from Chromosome 17q, the p53 gene from Chromosome 17p, and the SOD gene from Chromosome 21q is detected. Following denaturation of DNA at 94.degree. C., pairs of oligonucleotide probes, having a target-specific portion and a primer-specific portion, are allowed to anneal adjacent to each other on target nucleic acids and ligate to one another (in the absence of mismatches). This ligase detection reaction is carried out with Tth ligase at a hybridization/ligation temperature of 65.degree. C. which is well below the T.sub.m values of 75.degree. C. for the oligonucleotide probes. Next, the ligation product sequences are simultaneously amplified by PCR using Taq polymerase and two common primers complementary to the primer-specific portion, one of which is fluorescently labeled. This maintains the proportionality of the target sequences initially present in the sample. The extension products are then digested with HaeIII and Hinp1I which releases fluorescently labeled fragments of unique sizes for each target sequence present in the sample. The digestion products are separated and analyzed on an Applied Biosystems, Inc. (Foster City, Calif.) 373A DNA Sequencer. The peak heights and areas are related to the relative copies of genes present in the initial target sample.

FIG. 11 is a schematic diagram, depicting a problem which can be encountered with the allele-specific LDR/PCR process. While a PCR/LDR process is very powerful, there may be circumstances where a multiplexed allele-specific LDR/PCR process of the present invention would be preferred. The concept is to have one or more sets of LDR oligonucleotide probes, each set characterized by (a) a first oligonucleotide probe, having a target-specific portion and a 5' upstream primer-specific portion, and (b) a second oligonucleotide probe, having a target-specific portion and a 3' downstream primer-specific portion. As shown in step 1 of FIG. 11, the LDR oligonucleotide probes anneal adjacent to each other on the target sequence. An LDR reaction using thermostable ligase (black dot) would form a ligation product sequence provided there is perfect complementarity at the ligation junction. In step 2, the ligation product sequences are PCR amplified with primer sets, each set characterized by (a) an upstream primer containing the same sequence as the 5' upstream primer-specific portion of a ligation product sequence and (b) a downstream primer complementary to the 3' downstream primer-specific portion of that ligation product sequence. The primers are shown as black lines in step 2. If one primer is fluorescently labeled, it will generate a fluorescent product which may be detected in a variety of detection schemes. For the LDR/PCR process to be specific, a PCR extension product should not be formed in the absence of a ligation event. Unfortunately, the possibility exists for polymerase to extend the first LDR oligonucleotide probe (off normal target), forming a

control 5 of 10 Done

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BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a flow diagram depicting a primary PCR/secondary PCR/LDR process for detection of germline mutations, such as point mutations, by electrophoresis or capture on an addressable array. Note that the term "zip-code" which appears in FIG. 1 and other

drawings refers to a sequence specific to a subsequently used primer or probe but not to either the target sequence or other genome sequences.

FIG. 2 is a flow diagram depicting a primary PCR/secondary PCR/LDR process for detection of biallelic polymorphisms by electrophoresis or capture on an addressable array.

FIG. 3 is a flow diagram depicting a primary PCR/secondary PCR/LDR process for detection of cancer-associated mutations by electrophoresis or capture on an addressable array.

FIG. 4 is a schematic diagram depicting a primary PCR/secondary PCR/LDR process for detection of biallelic polymorphisms.

FIG. 5 is a schematic diagram depicting a primary PCR/secondary PCR/LDR process for detection of allelic differences using LDR oligonucleotide probes which distinguish all possible bases at a given site.

FIG. 6 is a schematic diagram depicting a primary PCR/secondary PCR/LDR process for detection of the presence of any possible base at two nearby sites using LDR oligonucleotide probes which distinguish all possible bases at a given site.

FIG. 7 is a schematic diagram depicting a primary PCR/secondary PCR/LDR process for detection of cancer-associated mutations at adjacent alleles.

FIG. 8 is a flow diagram depicting an LDR/PCR process with and without restriction endonuclease digestion using electrophoresis detection.

FIG. 9 is a flow diagram depicting an LDR/PCR process using detection on an addressable array using gene-specific addresses.

FIG. 10 is a schematic diagram depicting an LDR/PCR process for multiplex detection of gene amplifications and deletions.

FIG. 11 is a schematic diagram depicting an allele specific problem for an LDR/PCR process.

FIG. 12 is a schematic diagram depicting a solution for the allele specific problem for an LDR/PCR process which is shown in FIG. 11.

FIG. 13 is a flow diagram depicting an LDR/PCR process with an intermediate exonuclease digestion phase for detection of biallelic polymorphisms by electrophoresis or capture on an addressable array.

FIG. 14 is a flow diagram depicting an LDR/PCR process with an intermediate exonuclease digestion phase for detection of cancer-associated mutations by electrophoresis or capture on an addressable array.

FIG. 15 is a schematic diagram depicting an LDR/PCR process with an intermediate

Fig. 3 of 95 Done

Sent from my iPhone

On Feb 24, 2017, at 6:57 AM, Francis Barany <barany@med.cornell.edu> wrote:

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> Sent from my iPhone

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>
<Favis_Gerry_Cheng_Barany_2005_chapter.pdf>

Subject 13236805

From Monib Zirvi <matzirvi@yahoo.com>

To: <barany@med.cornell.edu>,
<roger.chin@lw.com>,
<mpearson@akingump.com>,
Valerie Cross Dorn
<vlc1@cornell.edu>,
<bjk44@cornell.edu>

Date Feb 24, 2017 at 11:11 AM

Sent from my iPhone

13236805.pdf

Subject Zipcode and target sequence in control

From Monib Zirvi <matzirvi@yahoo.com>

To: <barany@med.cornell.edu>, <roger.chin@lw.com>, <mpearson@akingump.com>, Valerie Cross Dorn <vlc1@cornell.edu>, <bjk44@cornell.edu>, <Doug.Lumish@lw.com>

Date Feb 24, 2017 at 11:12 AM

Sent from my iPhone

Subject Control with perfectly match to addressable array portion and extra target specific portion

From Monib Zirvi <matzirvi@yahoo.com>

To: <barany@med.cornell.edu>, <roger.chin@lw.com>, <mpearson@akingump.com>, Valerie Cross Dorn <vlc1@cornell.edu>, <bjk44@cornell.edu>

Date Feb 24, 2017 at 11:16 AM

Sent from my iPhone

Subject '016 patent

From Monib Zirvi <matzirvi@yahoo.com>

To: Valerie Cross Dorn <vlc1@cornell.edu>

Cc: <barany@med.cornell.edu>, Matthew Pearson <mpearson@akingump.com>, <roger.chin@lw.com>

Date Feb 24, 2017 at 7:15 PM

Dear Valerie,

It occurred to me that when originally filed, this suit contained numerous patent ands claims and this was reduced at the Courts insistence. Knowing the Markman wording now, is it possible that infinium or beadchip products could infringe other claims in other patents such as '016 which were written to cover infinium?

Thanks for all of your efforts and explanations and a very productive phone meeting this morning.

Monib

Sent from my iPhone

Subject '016 patent

From Monib Zirvi <matzirvi@yahoo.com>

To: Valerie Cross Dorn <vlc1@cornell.edu>

Cc: <barany@med.cornell.edu>, Matthew Pearson <mpearson@akingump.com>, <roger.chin@lw.com>

Date Feb 25, 2017 at 10:51 AM

Dear Valerie,

It occurred to me that when originally filed, this suit contained numerous patents and claims and this was reduced at the Court's insistence. Knowing the Markman wording now, is it possible that infinium or beadchip products could infringe other claims in other patents such as '016 which were written to cover infinium?

In addition, our arrays need control locations on chips (fiducial controls) and quality controls for testing prior to use (test hybridizations with capture oligonucleotide probes which contain addressable sequences and labels but no target sequence, as demonstrated in Example 6) to know that the arrays are functional and operational prior to use. This is an essential component of the system and was part of all of the embodiments in the patent families and the wording in the Markman does not capture this use.

Monib

Thanks for all of your efforts and explanations and a very productive phone meeting this morning.

Monib

Sent from my iPhone

Subject Re: '016 patent

From Valerie Cross Dorn <vlc1@cornell.edu>

To: Monib Zirvi <matzirvi@yahoo.com>

Cc: barany@med.cornell.edu <barany@med.cornell.edu>, Matt Pearson <mpearson@akingump.com>, roger.chin@lw.com <roger.chin@lw.com>

Date Feb 25, 2017 at 4:17 PM

Monib, your thought is creative, but I don't think it will work. We asserted claim 1 of the '016 in our reduced set of 30 mandated by the court, and I believe all other claims in the '016 are dependent on that independent claim 1. That means all of the claims incorporate the limitations of claim 1, including a composite oligonucleotide, as well as other limitations. So, the challenges that Roger described related to the composite oligo will impede us with every claim of the '016.

I know the Markman ruling does not capture things that we consider essential, but we are constrained through any trial by the Markman ruling as it is currently worded. That means we will not be permitted to disagree with the Markman during the trial.

I hope this information helps. Valerie

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> Monib
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> Sent from my iPhone

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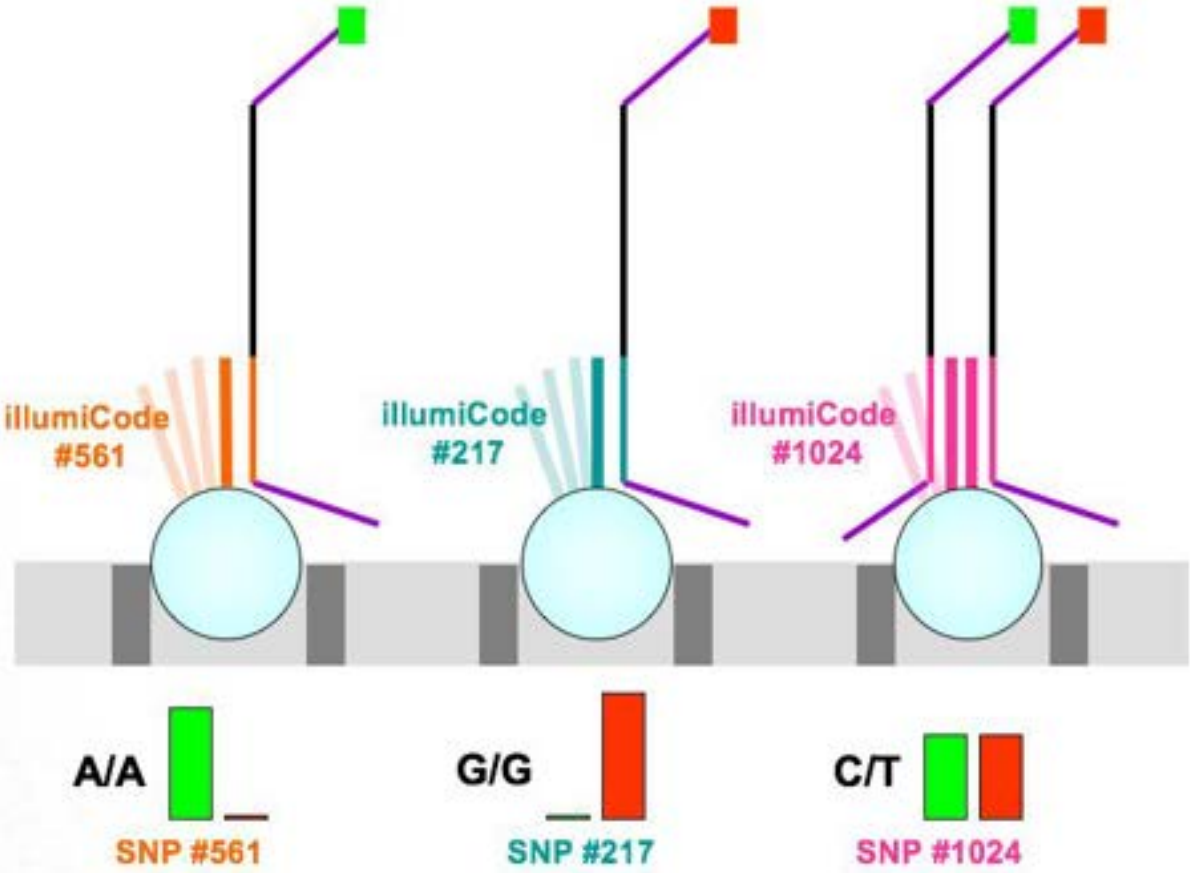
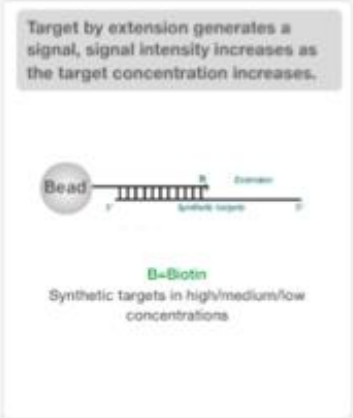
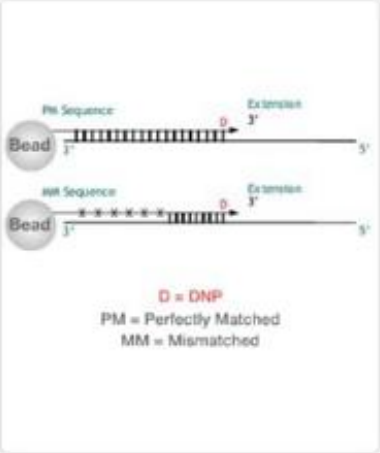
GoldenGate™ Assay
Hybridization to Universal IllumiCode™ Array



Term	Definition
	
Restoration Control *Sample-independent control*	The Restoration Control is specific to the Infinium HD FFPE Assay that requires formalin-fixed paraffin- embedded (FFPE)-derived DNA to be restored using Illumina's Infinium HD FFPE Restore Kit. The Restoration Control does not depend on the quality of sample DNA. It should show no activity for samples that have not been processed with the FFPE Restore kit. The Restoration Control uses a short oligo that has been spiked into the Infinium HD FFPE restore kit. Due to the chemistry of the Infinium HD FFPE Restore Kit, the control oligo will be available to bind to its complement on the BeadChip only if the restore process functions properly. Detection of reduced intensity of the Restoration Control may indicate that the DNA restoration process has been compromised. This control is detected in the green channel.
Sample-dependent Controls	The sample-dependent controls are used to evaluate assay performance across samples, and assess sample DNA quality. With the exception of Non-Specific Binding Controls, sample-dependent controls are specific to human DNA targets and cannot be used for interpretation of data obtained with non-human Infinium products, including non-human iSelect chips. In addition to poor sample quality, failure of any step in the assay (amplification, hybridization, X-stain) will result in depressed sample-dependent controls. Sample-dependent controls include Stringency Controls, Non-Specific Binding Controls, and Non-Polymorphic Controls.

Term	Definition
Stringency Controls *Sample-dependent control*	Stringency Controls test the stringency of the hybridization process. High stringency is achieved through increased temperature and optimized composition of the hybridization buffer. Perfect match (PM) controls are exactly complementary to their human DNA target, resulting in high signal intensities. In contrast, mismatch (MM) controls probes have mismatched nucleotides between target and probe to affect hybrid stability, and are expected to yield signals of much lower intensity under optimal stringency conditions. Performance of Stringency Controls is monitored in the red channel. 
Non-specific Binding Controls *Sample-dependent control*	Non-Specific Binding Controls are included to monitor the specificity with which amplified DNA hybridizes to the chip, assess sample DNA quality, and identify presence of non-human DNA. The probe sequences for Non-specific Binding Controls are complementary to bacterial sequences and should not hybridize to human sequences under standard hybridization conditions. Loss of the specificity of the assay and binding of non-human sequences complementary to control probes are expected to lead to increased signal intensities. These controls are monitored in both, the green and red channel, and should show intensities at background levels in both.
Non-polymorphic Controls *Sample-dependent control*	Non-Polymorphic Controls test the overall performance of the assay, from amplification to detection, by querying a particular base in a non-polymorphic region of the human genome. Non-polymorphic Controls are used to compare assay performance across different samples. One non-polymorphic control has been designed for each of the four nucleotides. A and T are monitored in the red channel, and C and G in the green channel.

Subject Re: '016 patent

From Monib Zirvi <matzirvi@yahoo.com>

To: Valerie Cross Dorn <vlc1@cornell.edu>

Cc: barany@med.cornell.edu <barany@med.cornell.edu>, Matt Pearson <mpearson@akingump.com>, roger.chin@lw.com <roger.chin@lw.com>

Date Feb 25, 2017 at 4:29 PM

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Date Feb 25, 2017 at 5:28 PM

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Date Feb 25, 2017 at 5:45 PM

Interchanging the two sides of Velcro does not make it not Velcro

Sent from my iPhone

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> <image1.png>

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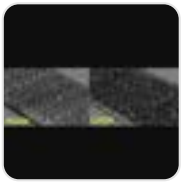

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Date Feb 26, 2017 at 9:45 AM

http://www.intellectualpropertylawfirms.com/legal-advice/patent-rights-and-laws-for-ideas.htm

Isn't this applicable regarding the 16 Zipcode sequences that Gunderson/Chee/Illumina claimed were their "original" invention?

Sent from my iPhone

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Subject Privileged and Confidential Re: WebEx meeting followup: Illumina-Cornell 1

From Francis Barany <barany@med.cornell.edu>

To: Roger Chin <Roger.Chin@lw.com>, Pearson, Matthew <mpearson@AKINGUMP.com>, Doug.Lumish@lw.com <Doug.Lumish@lw.com>, Finst, Rip <Rip.Finst@thermofisher.com>, Boyle, Sean <sean.boyle@thermofisher.com>, Brian Kelly <bjk44@cornell.edu>, Valerie Cross <vlc1@cornell.edu>

Cc: Monib Zirvi <matzirvi@yahoo.com>, Francis Barany <barany@med.cornell.edu>

Date Feb 27, 2017 at 3:38 PM

Dear Roger, Matthew, Doug, Rip, Sean, Valerie, and Brian,

Roger, thank you again for presenting a compelling set of arguments about the potential liabilities for Cornell in the current case. We see that you are a skilled litigator and trust you will be equally persuasive for our side when (if) this goes to trial.

Just to be clear, we have summarized the salient points of our perspective in the enclosed powerpoint, with a few new slides to better articulate the case for '016, Claim 1, (device claim). (Slides 4A-4F). These slides illustrate that capture sequences and zip code sequences are interchangeable, just like the "hooks" and "loops" in Velcro. It makes no difference whether the "hooks" or the "loops" are coupled to the solid support. In particular, once a composite oligonucleotide has been created and localized, it is clear the zip-

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specific portion of the sequence. Further, as shown in Fig. 4F, Illumina themselves had the identical diagram in their patent application, a full 7 years after Barany filed '917…

I understood your point about not mixing '917 and '470. However, my understanding is that when you articulate an invention in a patent application, you have the full term of that patent (17 or 20 years?) to provide substantiating evidence in support of the claims. The '917 patent clearly articulated the zip code array as an invention, in and of itself. Period. The '470 series, and many other follow-on patent build on, and provide additional support of the original claims. Thus, the '917 provides an unassailable example (6) of a zip code array capturing a zip code oligonucleotide, comprising of no additional target sequence. The '470 provides an additional example with the composite zip code – zip code primers used for co-amplifying primary LDR or PCR products.

For the other slides in the powerpoint:

Figs 3A-C articulate PCR-LDR, why it is superior to other approaches for identifying insertion or deletion mutations, and why a PCR-gap-LDR approach would give false-positive signal. There was a valid reason why in the prosecution history of the '917 patent, in the context of mutation detection, we preferred PCR-LDR over PCR-gap-LDR.

Figs 4A-4F described above.

Figures 5A-5C, 6 show the different bead arrays, including Infinium designs. Importantly, bead arrays are simply an assembly of random beads. Only by including zip codes do they become addressable arrays. If Illumina did not think that was important, then why did they try to patent the zip code sequences, including plagiarizing ours for their first 16? If they are just "hybridization arrays", why don't they show the judge how that would work without the zip code sequences?

Figures 7-9B are variations of LDR-PCR, including the example of hybridizing a non-target

containing composite zip code primer to the array (9B).

Figures 10A-11B are variations of PCR-PCR, including the example of hybridizing a non-target containing composite zip code primer to the array (11B).

Figures 12A-12C are examples of LDR-PCR or gap-LDR-PCR with zipcode capture. Here we show there is minimal and insufficient difference between LDR-PCR and gap-LDR-PCR for detecting SNPs. This is in contrast to the example of PCR-LDR vs. PCR-gap-LDR for mutation detection, especially insertions in repeat regions.

Figures 13-15 are DASL and Infinium Assays.

Figures 16-19 are examples of other variations of PCR–LDR, and LDR-PCR.

Figures 20-25 illustrate that the Infinium chips are fully zip code arrays, and can function in a properly designed PCR-LDR assay – as articulated in the '917 series of patents. That the arrays contain extra DNA is irrelevant. They are functionally zip code arrays.

Hope this is helpful to you.

Best,

Francis & Monib

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

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Latham & Watkins LLP

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Comments_Zip_code_array_variations_…

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Subject Privileged and Confidential Re: WebEx meeting followup: Illumina-Cornell 2

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Cc: Monib Zirvi <matzirvi@yahoo.com>, Francis Barany <barany@med.cornell.edu>

Date Feb 27, 2017 at 3:40 PM

Dear Roger, Matthew, Doug, Rip, Sean, Valerie, and Brian,

Perhaps you saw the Academy Awards last night, with an ad from the New York Times, beginning with "The truth is our nation is more divided than ever," that changes to "The truth is alternative facts are lies." The ad repeats different versions of the "The truth is..." as the voices speed up and get louder. The ad closes with: “The truth is hard. The truth is hard to find. The truth is hard to know. The truth is more important now than ever”. https://www.youtube.com/watch?v=gY0Fdz350GE

Just as Roger presented some potential issues on the Cornell side, there are some inconvenient truths that present serious liabilities on the Illumina side. Consider the following:

The first 16 “Illumacodes”, i.e. zip codes

were created by Barany and Zirvi in February 1999 at Cornell (as well as thousands of other zip codes). The Barany Lab first used the term “zip

codes). The Barany Lab first used the term "zip codes" in the 1994 grant application, and subsequently in the '917 and '470 patents. Contrary to Illumina propaganda, no other group used the term to describe this unique set of primers and probes in molecular biology. In short, zip-codes are the "operating system" of molecular biology, with PCR-LDR, LDR-PCR, PCR-PCR-LDR are the equivalent of Apps.

In May 1999, Gunderson and Chee signed a false declaration that they invented "adapters" after reading WO 97/31256.

In Nov, 1999 a Joint Development Agreement was signed by Illumina and ABI.

In Feb and March 2000, numerous copycat attempts were made by Illumina to re-patent the ideas of another, including combining ligase detection reaction with universal array capture. False declarations were signed yet again.

In July 2000, SEC paperwork was signed with oaths and declarations as well.

In August 2000 Gunderson/Chee/Illumina filed false paperwork and oaths to the USPTO claiming to have invented the 16 original "Illumacodes", as well as additional zipcode sequences.

These sequences were used to create derivative works and were misappropriated.

The sequences and their derivatives were used to create and test and market products including Sentrix Universal Array Matrix and Goldengate/DASL assays.

These literally infringed Cornell/Barany IP and thus were allegedly fraudulent source of revenue presented in 10K and other forms filed with the SEC for years.

As such, there is clearly the potential for Illumina to be the subject of an SEC fraud investigation if the above details are presented as a complaint to the SEC – a significant potential liability to Illumina,

which may include negative outcomes such as large fines, negative publicity, investigation of the CSO and CEO for their roles in said fraudulent patent submissions, and adverse effects on their stock price.

In any negotiations, it is important that Illumina be aware of all potential liabilities so they recognize it is in their best interest to negotiate a fair and just settlement.

And, if you watched the surprise ending to the Oscars, sometimes, the “David” wins.

With best wishes,

Francis & Monib

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

This email may contain material that is confidential, privileged and/or attorney work product for the sole use of the intended recipient. Any review, disclosure, reliance or distribution by others or forwarding without express permission is strictly prohibited. If you are not the intended recipient, please contact the sender and delete all copies including any attachments.

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Latham & Watkins LLP

<Mail Attachment.eml>

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Date Feb 27, 2017 at 4:09 PM

Figure 4 clearly shows that Barany '016 and Infinium are insubstantial different. A welding mixture which contained Manganese instead of Magnesium was found to be equivalent by a Jury and I have a high degree of confidence that a jury will be able to see how equivalent this situation is too.

Monib Zirvi

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[redacted]
barany@med.cornell.edu

barany@med.cornell.edu

[redacted]

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<Mail Attachment.eml>

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<Comments_Zip_code_array_variations_v06_Fig4A-F.pdf>
<Comments_Zip_code_array_variations_v06.pdf>
<Comments_Zip_code_array_variations_v06.pptx>

Subject Re: Privileged and Confidential Re: WebEx meeting followup: Illumina-Cornell 2

From Monib Zirvi <matzirvi@yahoo.com>

To: Francis Barany <barany@med.cornell.edu>

Cc: Roger Chin <Roger.Chin@lw.com>, Pearson, Matthew <mpearson@AKINGUMP.com>, Doug.Lumish@lw.com <Doug.Lumish@lw.com>, Finst, Rip <Rip.Finst@thermofisher.com>, Boyle, Sean <sean.boyle@thermofisher.com>, Valerie Cross <vlc1@cornell.edu>, Brian Kelly <bjk44@cornell.edu>

Date Feb 28, 2017 at 7:50 AM

Please watch this video.

The truth matters.

http://partners.wsj.com/face-of-real-news/john-carreyrou-investigative-reporter/

No amount of intimidation, IPRs or Ex Partes can bury the truth...

Monib

Sent from my iPhone

On Feb 27, 2017, at 3:40 PM, Francis Barany <barany@med.cornell.edu> wrote:

Dear Roger, Matthew, Doug, Rip, Sean, Valerie, and Brian,

Perhaps you saw the Academy Awards last night, with an ad from the New York Times, beginning with "The truth is our nation is more divided than

ever," that changes to "The truth is alternative facts are lies." The ad repeats different versions of the "The truth is..." as the voices speed up and

"The truth is..." as the voices speed up and get louder. The ad closes with: "The truth is hard. The truth is hard to find. The truth is hard to know. The truth is more important now than ever". https://www.youtube.com/watch?v=gY0Fdz350GE

Just as Roger presented some potential issues on the Cornell side, there are some inconvenient truths that present serious liabilities on the Illumina side. Consider the following:

The first 16 "Illumacodes", i.e. zip codes were created by Barany and Zirvi in February 1999 at Cornell (as well as thousands of other zip codes). The Barany Lab first used the term "zip codes" in the 1994 grant application, and subsequently in the '917 and '470 patents. Contrary to Illumina propaganda, no other group used the term to describe this unique set of primers and probes in molecular biology. In short, zip-codes are the "operating system" of molecular biology, with PCR-LDR, LDR-PCR, PCR-PCR-LDR are the equivalent of Apps.

In May 1999, Gunderson and Chee signed a false declaration that they invented "adapters" after reading WO 97/31256.

In Nov, 1999 a Joint Development Agreement was signed by Illumina and ABI.

In Feb and March 2000, numerous copycat attempts were made by Illumina to re-patent the ideas of another, including combining ligase detection reaction with universal array capture. False declarations were signed yet again.

In July 2000, SEC paperwork was signed with oaths and declarations as well.

In August 2000 Gunderson/Chee/Illumina filed false paperwork and oaths to the USPTO claiming to have invented the 16 original "Illumacodes", as well as additional zipcode sequences.

These sequences were used to create derivative works and were misappropriated.

The sequences and their derivatives were used to create and test and market products including Sentrix Universal Array Matrix and Goldengate/DASL assays.

These literally infringed Cornell/Barany IP and thus were allegedly fraudulent source of revenue presented in 10K and other forms filed with the SEC for years.

As such, there is clearly the potential for Illumina to be the subject of an SEC fraud investigation if the above details are presented as a complaint to the SEC – a significant potential liability to Illumina, which may include negative outcomes such as large fines, negative publicity, investigation of the CSO and CEO for their roles in said fraudulent patent submissions, and adverse effects on their stock price.

In any negotiations, it is important that Illumina be aware of all potential liabilities so they recognize it is in their best interest to negotiate a fair and just settlement.

And, if you watched the surprise ending to the Oscars, sometimes, the “David” wins.

With best wishes,

Francis & Monib

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

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Latham & Watkins LLP

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Subject Re: Privileged and Confidential Re: WebEx meeting followup: Illumina-Cornell 1B

From Francis Barany <barany@med.cornell.edu>

To: Roger Chin <Roger.Chin@lw.com>, Pearson, Matthew <mpearson@AKINGUMP.com>, Doug.Lumish@lw.com <Doug.Lumish@lw.com>, Finst, Rip <Rip.Finst@thermofisher.com>, Boyle, Sean <sean.boyle@thermofisher.com>, Valerie Cross <vlc1@cornell.edu>, Brian Kelly <bjk44@cornell.edu>

Cc: Monib Zirvi <matzirvi@yahoo.com>, Francis Barany <barany@med.cornell.edu>

Date Feb 28, 2017 at 10:25 AM

Dear Roger, Matthew, Doug, Rip, Sean, Valerie, and Brian,

Monib also pointed out a disconnect in the Markman definition of "addressable array-specific portion," address specific portion" and zip code portion" as these terms mean "portion of an oligonucleotide that selectively hybridizes to a complementary oligonucleotides located on an array, and does not hybridize to naturally occurring nucleic acids or to other oligonucleotides located on an array.

Yet, as clearly evidenced in Table 2 and 3 of the '917 application, it is the "zip code" oligonucleotide that is immobilized to the solid support. That immobilization of the "zip code portion" may be via a direct link, via a spacer, or via additional bases (such at dT10). For example, when the zip code is made of PNA, it is linked to the solid support (Table 2). I have enclosed other papers we have written to clearly show the oligonucleotide that is physically

linked to the array is called the "zip code".

How can a zip code portion that is on the array (like

How can a zip-code portion that is on the array (like a PNA) hybridize to a complementary oligonucleotide on an array? It can't move, it's already on the array. This makes no sense.

As articulated yesterday, zip code sequences can hybridize to their complements, independent of which one is immobilized to the solid support. When using Velcro strips to attach posters (i.e. oligonucleotides) to a wall (i.e. the solid support) it doesn't matter if the Velcro part on the wall has the hooks, and the Velcro on the poster has the loops, or if the Velcro part on the wall has the loops, and the Velcro on the poster has the hooks.

What makes our zip codes unique is that each velcro pair is unique, such that a given poster always goes to the right spot on the wall, and the design accelerates that process, much like a Google search engine hones into the right branches of the internet to find exactly the web site you need.

Hope this is helpful,

Best,

Francis

[redacted]
barany@med.cornell.edu

[redacted]

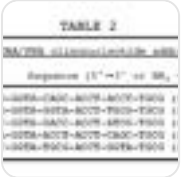
> On Feb 27, 2017, at 4:09 PM, Monib Zirvi
>
> <matzirvi@yahoo.com> wrote:
>
> Figure4 clearly shows that Barany '016 and Infinium are insubstantial different. A welding mixture which contained Manganese instead of

Magnesium was found to be equivalent by a Jury and I have a high degree of confidence that a jury will be able to see how equivalent this situation is too.

Monib Zirvi

Sent from my iPhone

View less



Gerry_et_al_Universal_Array_1999.pdf

Favis_Universal DNA array detection of …

Pingle_PCR_LDR_Univ_Array_Review…

Subject Zipcodes

From Monib Zirvi <matzirvi@yahoo.com>

To: Francis Barany <barany@med.cornell.edu>

Cc: <roger.chin@lw.com>, Matthew Pearson <mpearson@akingump.com>, Valerie Cross Dorn <vlc1@cornell.edu>

Date Mar 1, 2017 at 11:26 AM

On another note,

In addition to example 6 in '917...

I spent months with Herman Blok hybridizing complementary Zipcodes labeled only with fluorescent moieties (AND no target sequences) to Zipcode sequences coupled to various surfaces with either extra sequence or long linkers to PROVE that zipcode sequences worked. Without that experimentation, random arrays could not even be attempted with zipcode sequences, because the results would be unverifiable and uninterpretable. I believe testifying in front of a Judge and Jury will make this point clear. The ORIGINAL capture oligonucleotides in the Barany lab had NO target sequences.

Monib

Sent from my iPhone

On Mar 1, 2017, at 11:12 AM, Francis Barany <barany@med.cornell.edu> wrote:

> Talk then.
>
> FB
>
> Sent from my iPhone
>
> On Mar 1, 2017, at 1109 AM, Monib Zirvi <matzirvi@yahoo.com> wrote:

Call you at Noon

Sent from my iPhone

On Mar 1, 2017, at 10:48 AM, Francis Barany <barany@med.cornell.edu> wrote:

> Dear Monib,
>
> There's more, but not for email.
>
> I am still at home, will work out, shower, and head in.
>
> Call my cell when convenient for you if you like.
>
> Best,
>
> Francis
>
> [redacted]
> [redacted]
> barany@med.cornell.edu
>
> [redacted]
>
> On Mar 1, 2017, at 10:31 AM, Monib Zirvi <matzirvi@yahoo.com> wrote:
>
> Very interesting
>
> Sent from my iPhone
>
> On Mar 1, 2017, at 10:07 AM, Francis Barany <barany@med.cornell.edu> wrote:
>
> > Dear Monib,
> >
> > When searching for "SEC Applera Illumina "Tag Sequences"" I came across the enclosed document labeled:
> >
> > Affymetrix_vs_Illumina_1-04-cv-00901_357-2_Filed_02_05_2007.pdf

In it, it refers to

AFFYMETRIX'S LIST OF PRE-MARKED EXHIBITS,
INCLUDING DESIGNATIONS OF INTERROGATORIES AND
ANSWERS THERETO, THAT IT INTENDS TO OFFER AT TRIAL

Trail Exhibit 36 = Email re: Tag Sequences, dated 04/25/2000

This is probably an email within Illumina, that refers to the Tag sequences they are designing.

I found the original lawsuit:

Affymetrix Inc. v. Illumina Inc., 1:04-cv-00901

https://www.docketalarm.com/cases/Delaware_District_Court/1--04-cv-00901/Affymetrix_Inc._v._Illumina_Inc./

Other search on the internet for “SEC Illumina “Tag Sequences”” or “SEC Affymetrix “Tag Sequences”” did not reveal much useful — I downloaded some documents in case we need them with regards to Affymetrix.

Both companies had lots of exhibits, which I could not see, at the end of the day, the judge ruled the case dismissed “with prejudice", and each party was responsible for its own legal costs. That means the case is dismissed

permanently.

Please no speculations via email.

Have a great time in Florida.

Best,

Francis

[redacted]

barany@med.cornell.edu

[redacted]

<Affymetrix_vs_Illumina_1-04-cv-00901_357-2_Filed_02_05_2007.pdf>
<Affymetrix_SEC_10k_12_31_2003.pdf>
<Illumina, Inc_SEC_10K_12_31_2006.pdf>
<A unique and universal molecular barcode array_Stanford_2006.pdf>
<Affymetrix Introduces Genechip(R) Genflex(TM) Tag Array_04_18_2000.pdf>

Subject Privileged and Confidential Re: Zipcodes

From Francis Barany <barany@med.cornell.edu>

To: roger.chin@lw.com <roger.chin@lw.com>, Matthew Pearson <mpearson@akingump.com>, Valerie Cross <vlc1@cornell.edu>

Cc: Monib Zirvi <matzirvi@yahoo.com>, Francis Barany <barany@med.cornell.edu>

Date Mar 1, 2017 at 12:33 PM

Dear Roger, Matthew, and Valerie,

Following up on Monib's comment below, we do have some important questions for you to consider with regards to the original zip codes, and their derivatives.

We understand that the answer to some of these questions are privileged, but we want to make sure you provide those answers to Valerie, so that Cornell University has full knowledge of the timeline when Illumina took our zip codes, and their attempt to obfuscate it by calling it at least a dozen other names...

Please correct us if we are mistaken, but since there are 16 sequences that belong to Cornell, and the inventors who designed them, since it was never Illumina's property to begin with, we believe we should have full knowledge of their use and potentially other of our zip codes from our lists.

Thank you again for taking our concerns seriously.

Best,

Francis

[redacted]

[redacted] [redacted]
barany@med.cornell.edu

[redacted]

> On Mar 1, 2017, at 11:26 AM, Monib Zirvi <matzirvi@yahoo.com> wrote:
>
> On another note,
>
> In addition to example 6 in '917...
>
> I spent months with Herman Blok hybridizing complementary Zipcodes labeled only with fluorescent moieties (AND no target sequences) to Zipcode sequences coupled to various surfaces with either extra sequence or long linkers to PROVE that zipcode sequences worked. Without that experimentation, random arrays could not even be attempted with zipcode sequences, because the results would be unverifiable and uninterpretable. I believe testifying in front of a Judge and Jury will make this point clear. The ORIGINAL capture oligonucleotides in the Barany lab had NO target sequences.
>
> Monib
>
> Sent from my iPhone

In Illumina 60/180,810 Provisional, Filed Feb. 7, 2000:
"Illumina has developed Universal BeadArrays with 128 unique addresses that hybridize efficiently and with high specificity."

Questions:
Do you have the original 128 sequences in the '810 application?
Do they contain our 16 zip codes?

Do they contain any other or all of our zip codes from our 465 zip code list?

Illumina submits provisional application 60/135,123

(K. Gunderson) on May 20, 1999
Title: Addressing an Array using Sequence-Specific Adapters.
This is an attempt to re-patent our Universal arrays and zip code primers.

In response to question 11: “What are the immediate research plans of steps to be taken:”
Gunderson says “Research is ongoing. A set of 16 “adapters” is in use; set of 100 “adapters” will be prepared and tested in the near future
(Kevin Gunderson).

Questions:
Do you know if those 16 “adapter” sequences were the complements of our 16 zip codes?
Do you know if the additional 100 “adapters” were from our 465 zip code list?
If the additional 100 “adapters” were not from our 465 list, do you have the source code of the program they wrote to generate those extra 100?
Is the word “zipcode” in the original source code for choosing these 100?

Illumina submits provisional application 60/227,948 (M. Chee and K. Gunderson) on August 25, 2000:
Illumina submits full application 09/940,185 on August 27, 2001.

This application lists 4000 probes, of which the first 16 “IllumaCodes” are the complements of Barany’s 16 zipcodes, which were in the same order within the first 52 zipcodes in Barany's unpublished list of 465 zipcodes.

Questions:
Did Illumina provide the source code for the program they wrote for this patent application?
Were our original 16 zip codes or their complements entered in the source code of Illumina’s original program, or were the sequences added later?
Is the word “zipcode” in the original source code for choosing the first set of 4,000 “IllumaCodes”?
Is the word “zipcode” in the follow-up source code for choosing additional “IllumiCodes”?

for choosing additional "IllumiCodes"?

When looking at the evolution of the different source codes to create DMAP files, was zipcode always listed, and what explanatory words surround it?

In over a dozen documents filed to the USTPO and SEC, Illumina refers to our zip codes with the following terms:
"IllumaCode"
"IllumiCode"
"Tag Sequence"
"Universal Tag Sequence"
"Sentrix Universal Array"
"Adapter Sequence"
"Decoder binding ligand"
"Identifier binding ligand"
"Locus-specific oligonucleotide"
"Address"
"Zip code loci"

"zip-code"

Questions:
Do you have the initial documents where the word "zipcode" is first used by Illumina?
Do you have the initial documents where the words listed above e.g. IllumaCode, IllumiCode, Tag Sequence, Universal Tag Sequence, Sentrix Universal Array, Adapter Sequence, Decoder binding ligand, Identifier binding ligand, Locus-specific oligonucleotide, or Address -- is/are used to describe a "zipcode" sequence or zipcode array by Illumina?

In our '917 and follow on patents, we articulate methods of creating zipcode sequences by assembling 5 to 6 tetramer sequences to make 20 or 24-mer sequences. This can be done by starting with either our 36 tetramers, or tetramer complements.

Questions:
Do you know how many of the current 1 million or so

zip code sequences in use by Illumina comprise
of 20 bases in a row that match to any combination
of 5 of our 36 tetramers, or their complements?

View less

Subject INFRINGEMENT ANALYSIS

From Monib Zirvi <matzirvi@yahoo.com>

To: <barany@med.cornell.edu>

Cc: <roger.chin@lw.com>, Matthew Pearson <mpearson@akingump.com>, Valerie Cross Dorn <vlc1@cornell.edu>

Date Mar 2, 2017 at 10:58 AM

In this case they obviously copied and made insignificant alterations that would be obvious to anyone who is a POSA. They did not try to design around the patent, because the actual zip code sequences were identical and behaved identically. They even call them zip codes internally even in their software to keep track of the sequences and their X and Y locations. Putting target sequences on an array would not be considered an innovation by a POSA. Zip code sequences to capture complementary capture oligonucleotide probes (without target sequence in Example 6 and with target sequence in other embodiments) would obviously be the invention being covered by a patent.

Monib

http://www.sughrue.com/files/Publication/bf405fd0-6b2f-4c0c-a869-8f22577aaa98/Presentation/PublicationAttachment/966ae4db-bb96-4a16-8497-96c2be747837/infringement.htm

Sent from my iPhone

Subject Re: Privileged - models and videos of oligonucleotide arrays on the solid support

From Francis Barany <barany@med.cornell.edu>

To: Maria Kempe <maria.kempe@med.lu.se>

Cc: Valerie Cross <vlc1@cornell.edu>, Pearson, Matthew <mpearson@AKINGUMP.com>, Monib Zirvi <matzirvi@yahoo.com>, George Barany <barany@umn.edu>, Robert Hammer <rphammer@gmail.com>, Goldman Mike <Michael.Goldman@leclairryan.com>, Brian Kelly <bjk44@cornell.edu>, Francis Barany <barany@med.cornell.edu>

Date Mar 2, 2017 at 11:02 AM

Dear Maria,

Thank you for your kind offer to have Henrik continue to help. His videos were really extraordinary, and I am enclosing one for others who have not seen it.

In the meantime, I have also spent considerable time and money creating models of oligonucleotides on an array — kindly take a look of the enclosed pdf.

There have been some additional developments in the case, and the Universities will provide an update at the appropriate time.

I need to confer with Valerie with regards to your question, and we will put it on our agenda for the next time we speak.

Thanks for your patience, best,

Francis

[redacted]
barany@med.cornell.edu

[redacted]

On Mar 2, 2017, at 10:42 AM, Maria Kempe <maria.kempe@med.lu.se> wrote:

Dear Matthew and Francis,

I hope everything is going well. I wonder if you need any video clips in addition to the ones we did last year. With the term solid support accepted, the needs are maybe different? My brother Henrik has promised to help to do any additional movies that may be needed. If you need any more video clips, please let me know asap.

Best regards,
Maria

From: Pearson, Matthew <mpearson@AKINGUMP.com>
Sent: Friday, January 13, 2017 3:40 PM
To: 'George Barany'; Francis Barany (barany@med.cornell.edu); 'Robert Hammer'; Maria Kempe; 'Matthew Lubin'; 'Monib Zirvi'
Subject: Privileged

Privileged

Dear all –

I have attached a summary of the order we received this week from the judge in our case. Please let us know if you have any questions.

Happy New Year,
Matt Pearson

Matthew A. Pearson
AKIN GUMP STRAUSS HAUER & FELD LLP
Two Commerce Square | 2001 Market Street | Suite 4100 | Philadelphia,

PA 19103-7013 | USA | Direct: +1 215.965.1258 | Internal: 21258
Fax: +1 215.965.1210 | mpearson@akingump.com | akingump.com | Bio

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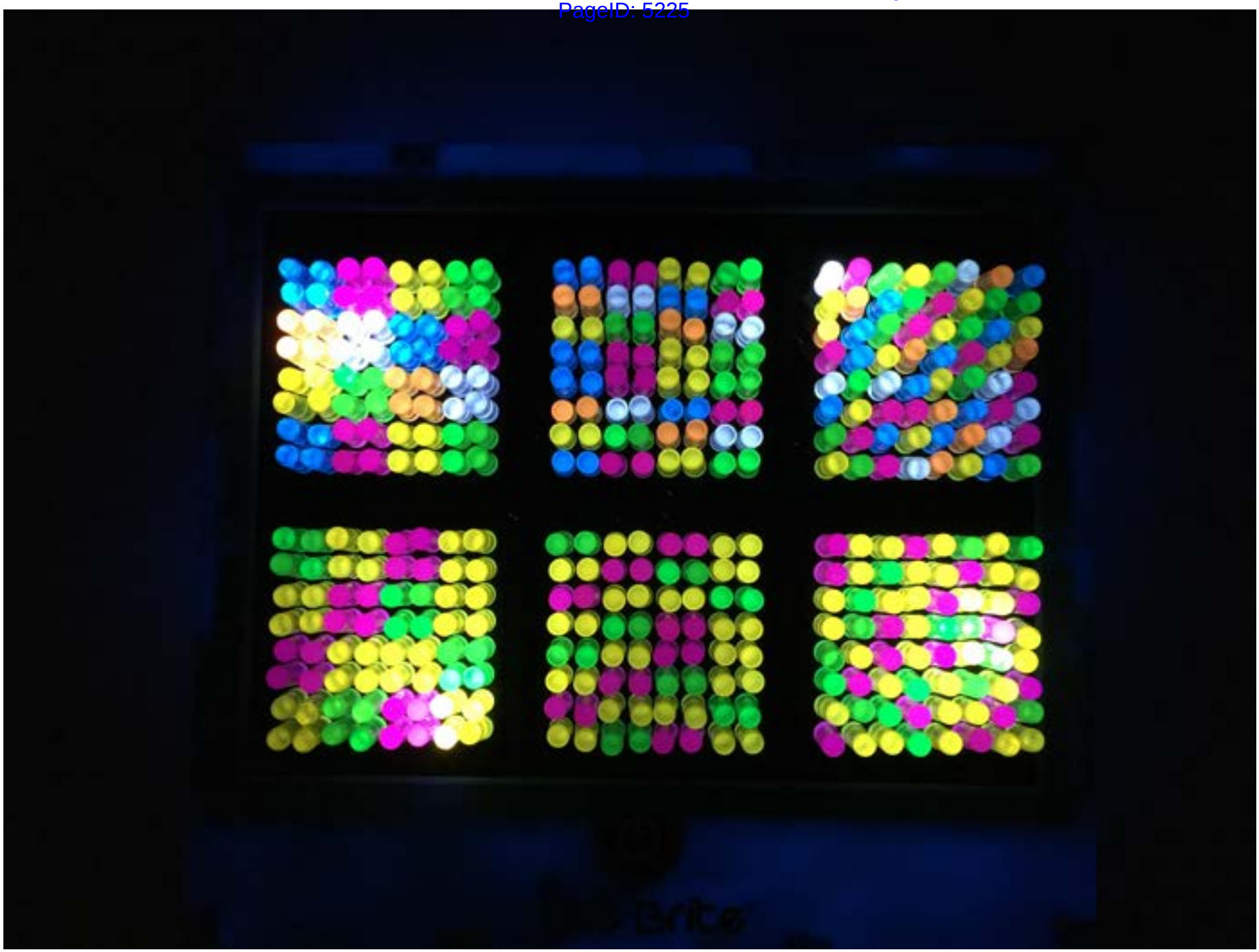
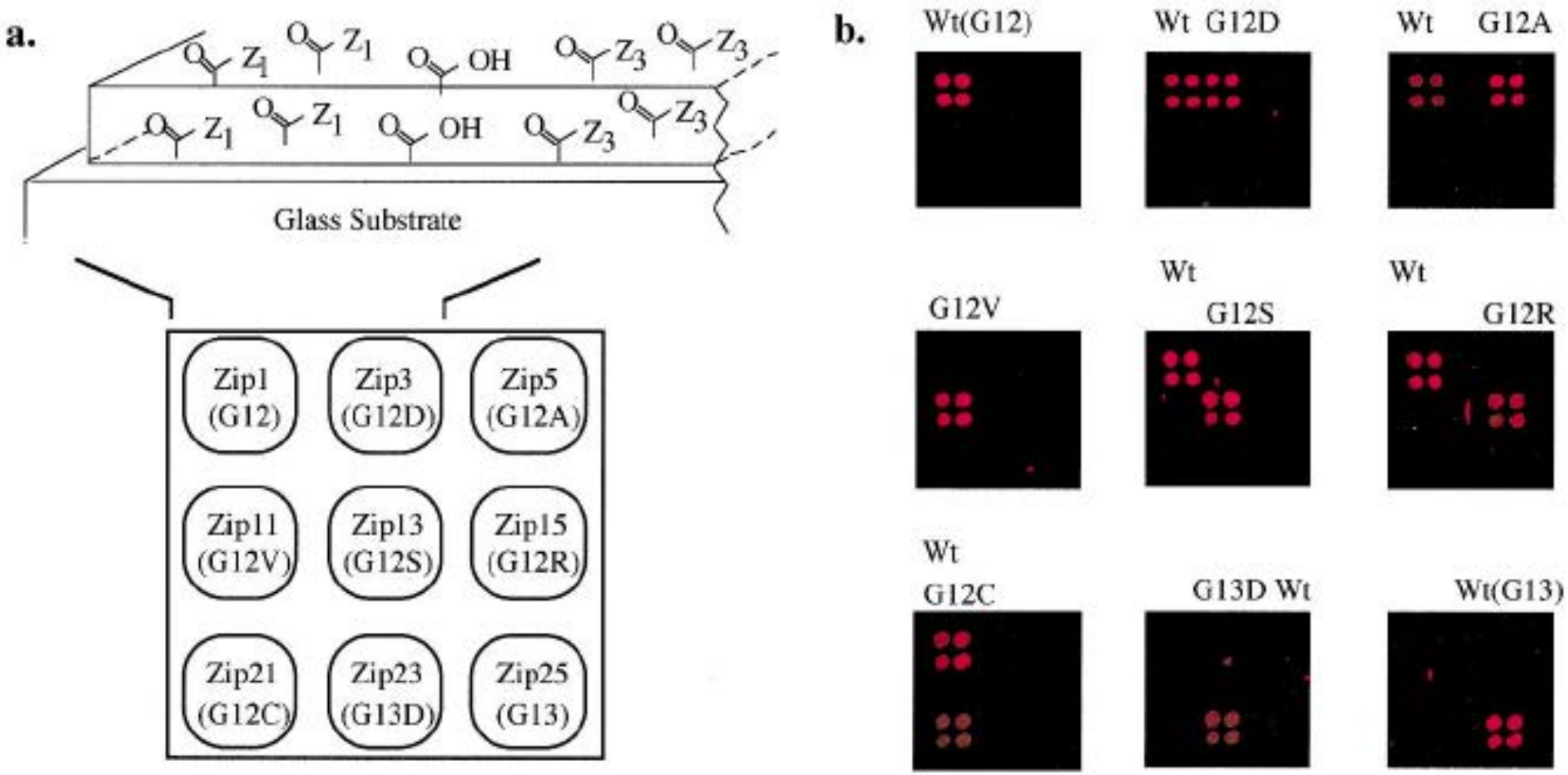
TheSecondMovie_E1_09_30_2016.mov

LiteBrite_pegs_02_23_2017_v01A.pdf




a.
Z1
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Glass Substrate
Zip1 (G12)
Zip3 (G12D)
Zip5 (G12A)
Zip11 (G12V)
Zip13 (G12S)
Zip15 (G12R)
Zip21 (G12C)
Zip23 (G13D)
Zip25 (G13)
b.
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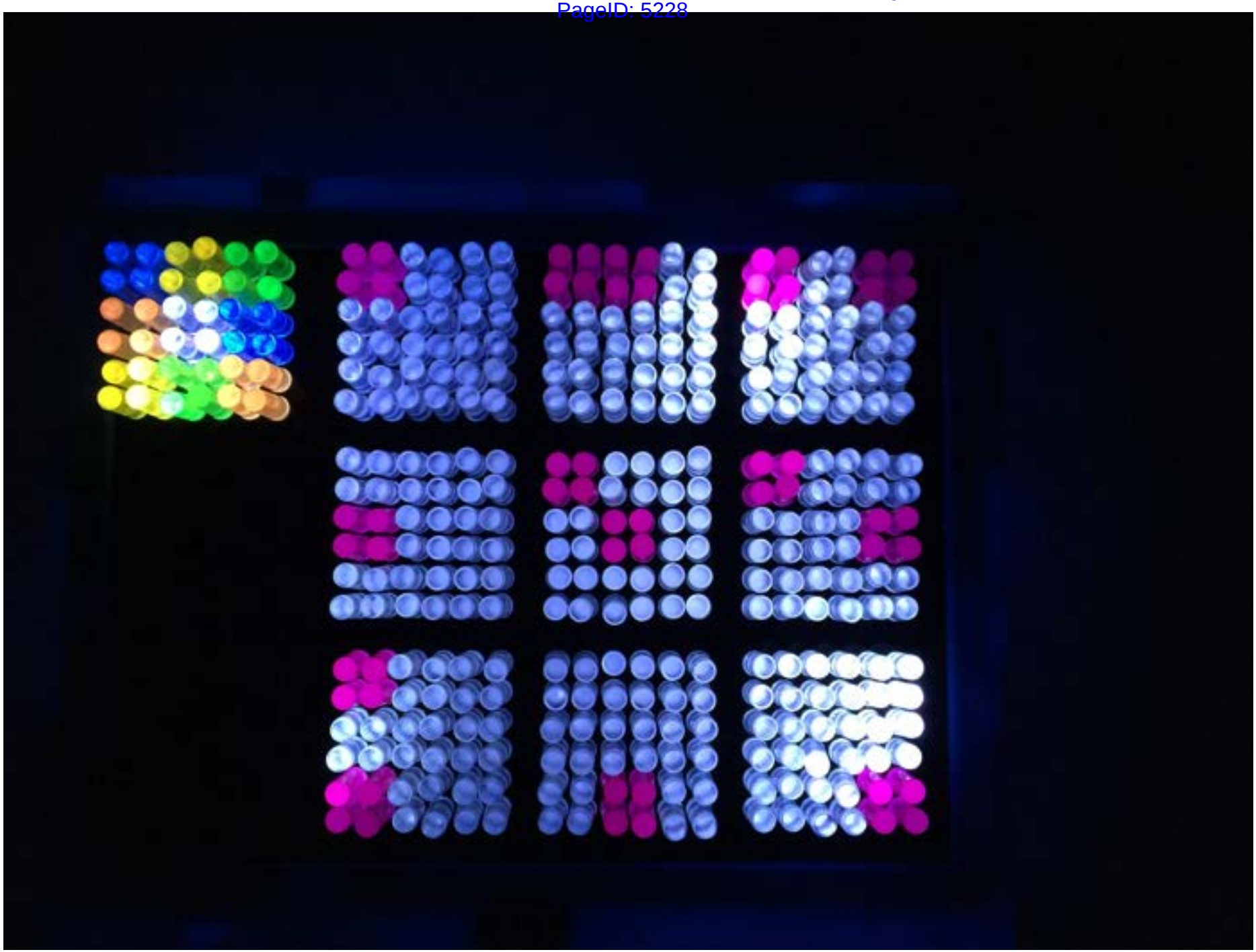

Subject Re: Privileged - models and videos of oligonucleotide arrays on the solid support

From Maria Kempe <maria.kempe@med.lu.se>

To: Francis Barany <barany@med.cornell.edu>

Cc: Valerie Cross <vlc1@cornell.edu>, Pearson, Matthew <mpearson@AKINGUMP.com>, Monib Zirvi <matzirvi@yahoo.com>, George Barany <barany@umn.edu>, Robert Hammer <rphammer@gmail.com>, Goldman Mike <Michael.Goldman@leclairryan.com>, Brian Kelly <bjk44@cornell.edu>

Date Mar 2, 2017 at 2:35 PM

Dear Francis,

Thanks for your quick reply. If you need some movies related to your array models, let me know.

All the best,
Maria

From: Francis Barany <barany@med.cornell.edu>
Sent: Thursday, March 2, 2017 4:57 PM
To: Maria Kempe
Cc: Valerie Cross; Pearson, Matthew; Monib Zirvi; George Barany; Robert Hammer; Goldman Mike; Brian Kelly; Francis Barany
Subject: Re: Privileged - models and videos of oligonucleotide arrays on the solid support

Dear Maria,

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I need to confer with Valerie with regards to your question, and we will put it on our agenda for the next time we speak.

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Francis

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

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Subject: Privileged

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Happy New Year,
Matt Pearson

Matthew A. Pearson
AKIN GUMP STRAUSS HAUER & FELD LLP
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19103-7013 | USA | Direct: +1 215.965.1258 | Internal: 21258
Fax: +1 215.965.1210 | mpearson@akingump.com | akingump.com | Bio

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Subject Re: Privileged - models and videos of oligonucleotide arrays on the solid support

From Francis Barany <barany@med.cornell.edu>

To: Maria Kempe <Maria.Kempe@med.lu.se>

Cc: Valerie Cross <vlc1@cornell.edu>, Pearson, Matthew <mpearson@AKINGUMP.com>, Monib Zirvi <matzirvi@yahoo.com>, George Barany <barany@umn.edu>, Robert Hammer <rphammer@gmail.com>, Michael Goldman <Michael.Goldman@leclairryan.com>, Brian Kelly <bjk44@cornell.edu>

Date Mar 2, 2017 at 3:14 PM

Dear Maria,

Will do.

Francis

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

> On Mar 2, 2017, at 2:35 PM, Maria Kempe <Maria.Kempe@med.lu.se> wrote:
>
> Dear Francis,
>
> Thanks for your quick reply. If you need some movies related to your array models, let me know.
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> All the best,

Maria

From: Francis Barany <barany@med.cornell.edu>
Sent: Thursday, March 2, 2017 4:57 PM
To: Maria Kempe
Cc: Valerie Cross; Pearson, Matthew; Monib Zirvi; George Barany; Robert Hammer; Goldman Mike; Brian Kelly; Francis Barany
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Francis

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barany@med.cornell.edu

[redacted]

On Mar 2, 2017, at 10:42 AM, Maria Kempe <maria.kempe@med.lu.se> wrote:

Dear Matthew and Francis,

I hope everything is going well. I wonder if you need any video clips in addition to the ones we did last year. With the term solid support accepted, the needs are maybe different? My brother Henrik has promised to help to do any additional movies that may be needed. If you need any more video

clips, please let me know asap.

Best regards,
Maria

From: Pearson, Matthew
<mpearson@AKINGUMP.com>
Sent: Friday, January 13, 2017 3:40 PM
To: 'George Barany'; Francis Barany (barany@med.cornell.edu); 'Robert Hammer'; Maria Kempe; 'Matthew Lubin'; 'Monib Zirvi'
Subject: Privileged

Privileged

Dear all –

I have attached a summary of the order we received this week from the judge in our case. Please let us know if you have any questions.

Happy New Year,
Matt Pearson

Matthew A. Pearson
AKIN GUMP STRAUSS HAUER & FELD LLP
[redacted] | [redacted] | [redacted] | [redacted]
[redacted] 19103-7013 | USA | Direct: +1 215.965.1258 | Internal: 21258
Fax: +1 215.965.1210 | mpearson@akingump.com | akingump.com | Bio

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The information contained in this e-mail message is intended only for the personal and confidential use of the recipient(s) named above. If you have received this communication in error, please notify us immediately by e-mail, and delete the original message.

View less

Subject Zipcodes in Infinium and Goldengate admitted by Walt

From Monib Zirvi <matzirvi@yahoo.com>

To: <barany@med.cornell.edu>, <roger.chin@lw.com>, <Rip.Finst@thermofisher.com>, <mpearson@akingump.com>, <Doug.Lumish@lw.com>, Valerie Cross Dorn <vlc1@cornell.edu>, <sean.boyle@thermofisher.com>, <bjk44@cornell.edu>

Date Mar 3, 2017 at 9:12 PM

Straight from the horse's mouth. (CSO David Walt)

Monib Zirvi

Sent from my iPhone

614-637%20Very%20High%20Density…

Subject Illumina started from zipcodes and still is completely dependent on them

From Monib Zirvi <matzirvi@yahoo.com>

To: Valerie Cross Dorn <vlc1@cornell.edu>, <sean.boyle@thermofisher.com>, <roger.chin@lw.com>, <Rip.Finst@thermofisher.com>, <mpearson@akingump.com>, <barany@med.cornell.edu>, <Doug.Lumish@lw.com>, <bjk44@cornell.edu>

Date Mar 3, 2017 at 9:14 PM

SNP Genotyping We are designing our first product based on the Array of Arrays for SNP genotyping. The first SNP genotyping assay format that we intend to commercialize will be PE Biosystems' proprietary OLA ZipCode assay format. This assay format enables the creation of a universal Array of Arrays that can be used to analyze any set of SNPs. We expect to commercialize our first product using this assay format in 2001. We plan to extend our BeadArray technology to create products using other assay formats. We expect one or more of these additional assay formats to be available on the Array of Arrays in 2002.

https://www.sec.gov/Archives/edgar/data/1110803/0001012870-00-001863.txt

Sent from my iPhone

Subject illuminasnpgenotyping

From Monib Zirvi <matzirvi@yahoo.com>

To: Valerie Cross Dorn
<vlc1@cornell.edu>,
<sean.boyle@thermofisher.com>,
<roger.chin@lw.com>,
<Rip.Finst@thermofisher.com>,
<mpearson@akingump.com>,
<barany@med.cornell.edu>,
<Doug.Lumish@lw.com>,
<bjk44@cornell.edu>

Date Mar 3, 2017 at 11:23 PM

Illumina's own marketing brochure explaining Infinium and the fact that DMAP files contain the "address" sequence and location of each bead. The DLL files for DMAP doesn't call them address. They call them Zipcode.

Sent from my iPhone

illuminasnpgenotyping.pdf

Illumina SNP Genotyping Technologies BeadArray and BeadChip Platform

SNP Genotyping Assay and SNP Multiplexing Level per Sample

- GoldenGate Assay

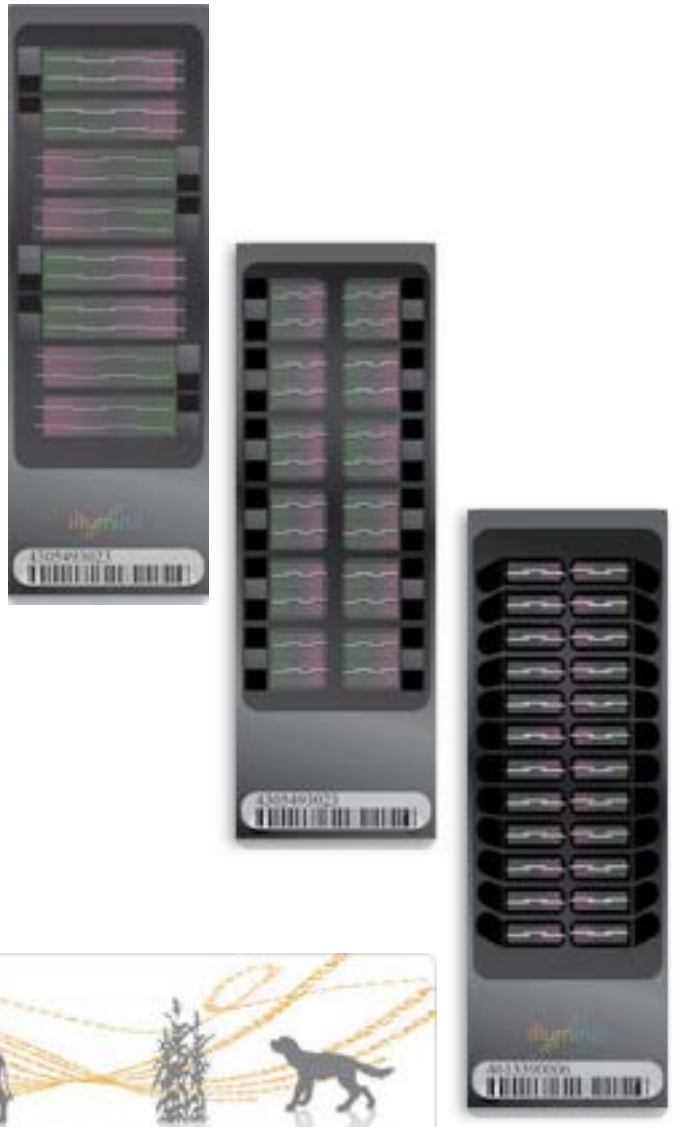
  OPA synthesis containing 48, 96, 144, 192, 384, 768, 1536, or 3072-plex SNPs per sample assay

- Infinium Assay

  Custom made iSelect chips to assay 3072 up to 1M SNPs per sample.

Infinium products targeted toward Agricultural markets

- BovineHD BeadChip
  - 8 samples, 777,962 SNPs
- BovineSNP50 BeadChip
  - 24 samples, 54,609 SNPs
- CanineHD BeadChip
  - 12 samples, 172,115 SNPs
- OvineSNP50 BeadChip
  - 12 samples, 54,241 SNPs
- PorcineSNP60 BeadChip
  - 12-samples, 62,163 SNPs
- MaizeSNP50 BeadChip
  - 24 samples, 56,110 SNPs
- iSelect Custom Panels



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iSelect BeadChip Formats and Supported Marker Densities

BeadChip Format	**24-sample**	**12-sample**	**4-sample**
Previous plex range	**3,072 – 60,800**	**60,801 – 200,000**	**n/a**
New plex range	**3,072 – 90,000**	**90,001 – 250,000**	**250,001 – 1M**
Add-on content range*	**Up to limit of 90,000**	**Up to limit of 250,000**	**Up to limit of 1M**

***Add-on content range allowed = (maximum attempted beadtypes on BeadChip) MINUS (existing beadtypes in original pool)**

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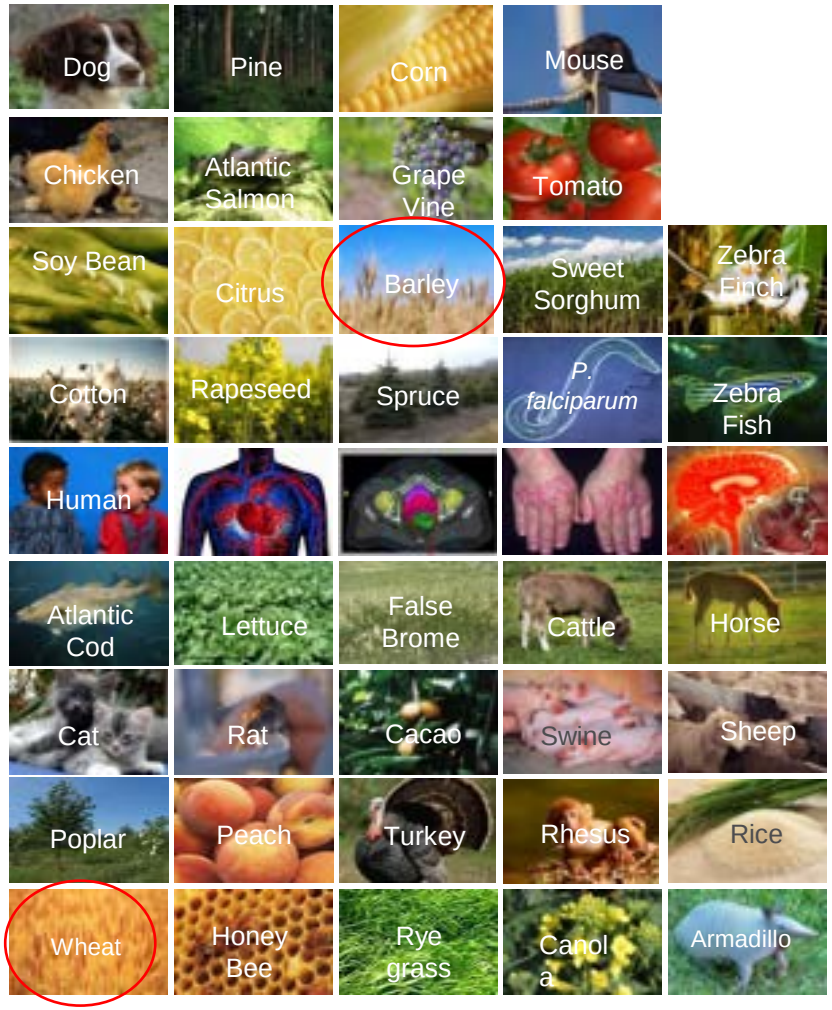
Custom Genotyping on the Infinium Assay



Applications

- Genome-wide selection
- Genetic Prediction
- SNP discovery
- Commercial Agriculture screening panels
- Targeted follow-up studies after GWAS
- Targeted disease panels
- Targeted rare variant panels
- Sample QC and tracking panels
- Consumer Genomics
- Forensics

The Right Content Lets You Capture More Biology

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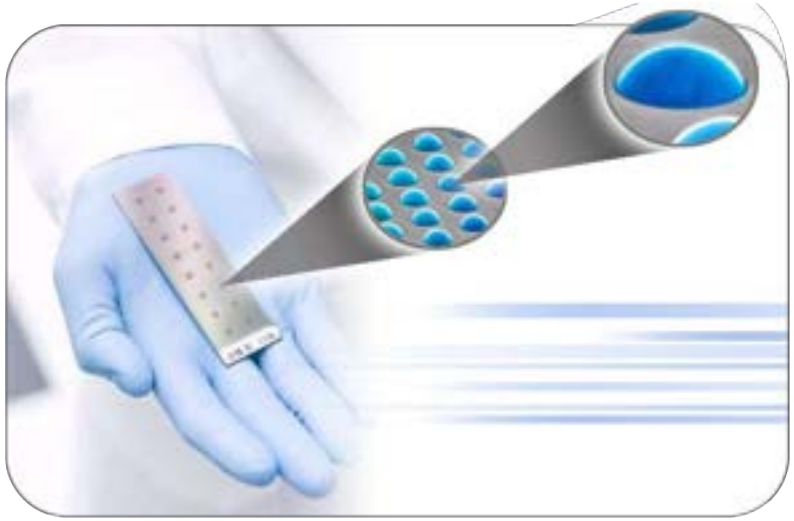
BeadArray technology and BeadChip manufacturing



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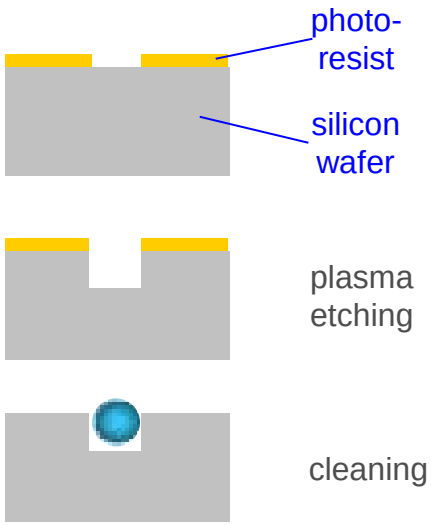
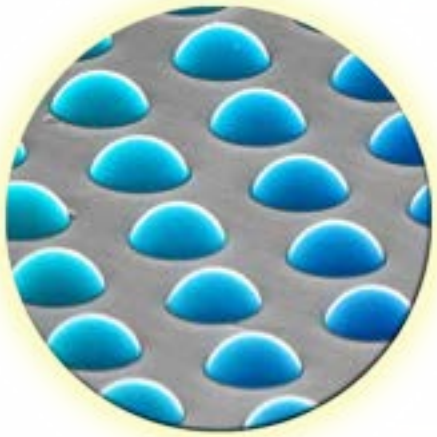
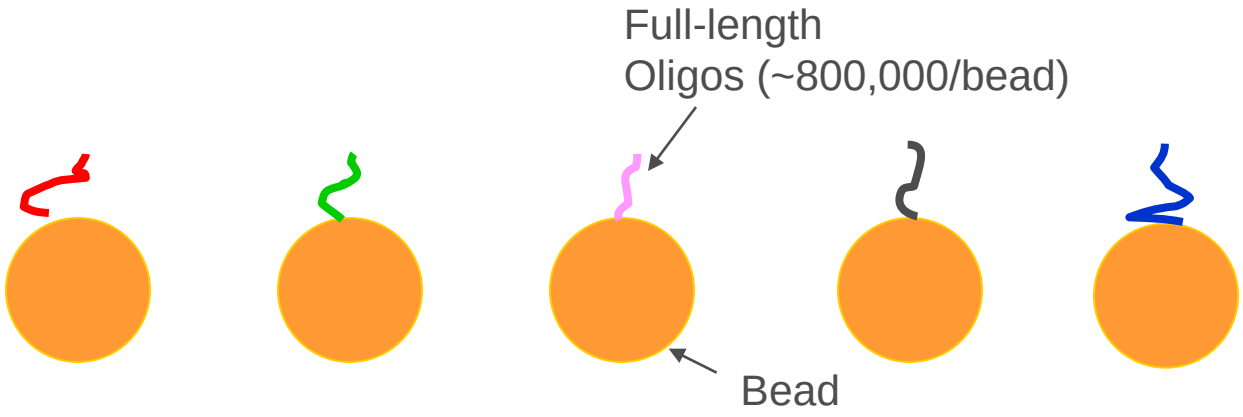
Microfabrication of BeadChip Wells





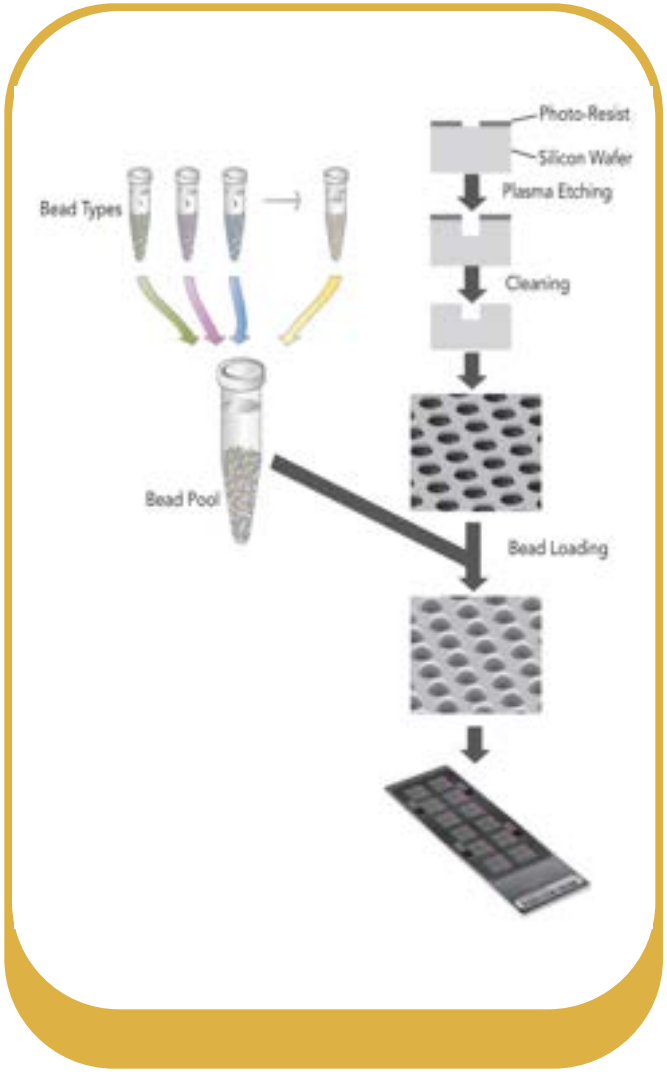
2 µm beads in wells

Beads and BeadTypes

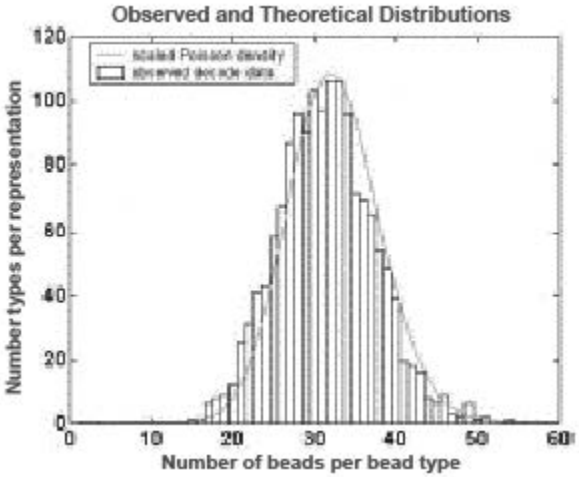


Redundancy: average of ~15 beads per beadtype

Bead Preparation and Array Production



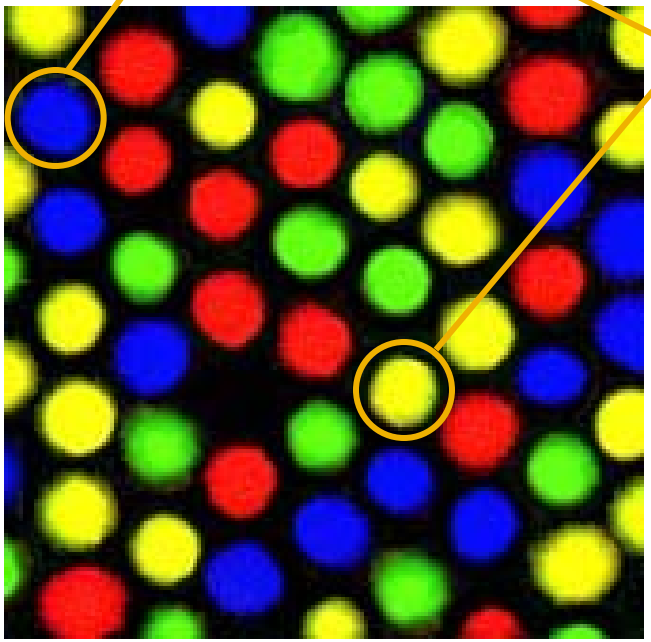
- Unique oligo for each bead type
- Bead Pool can be > 1,000,000 bead types
- Random self-assembly of beads
- Average ~15 beads per beadtype
- Functional validation of array



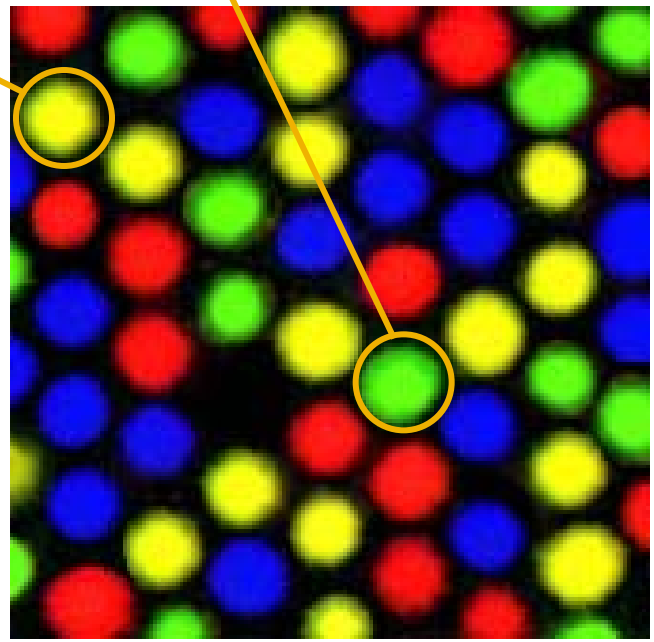
Bead Decoding

Example: 16 Bead Types

Decoder Oligo	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Decode hyb 1																



Decoder hybridization 1



Decoder hybridization 2

Generating a .dmap file

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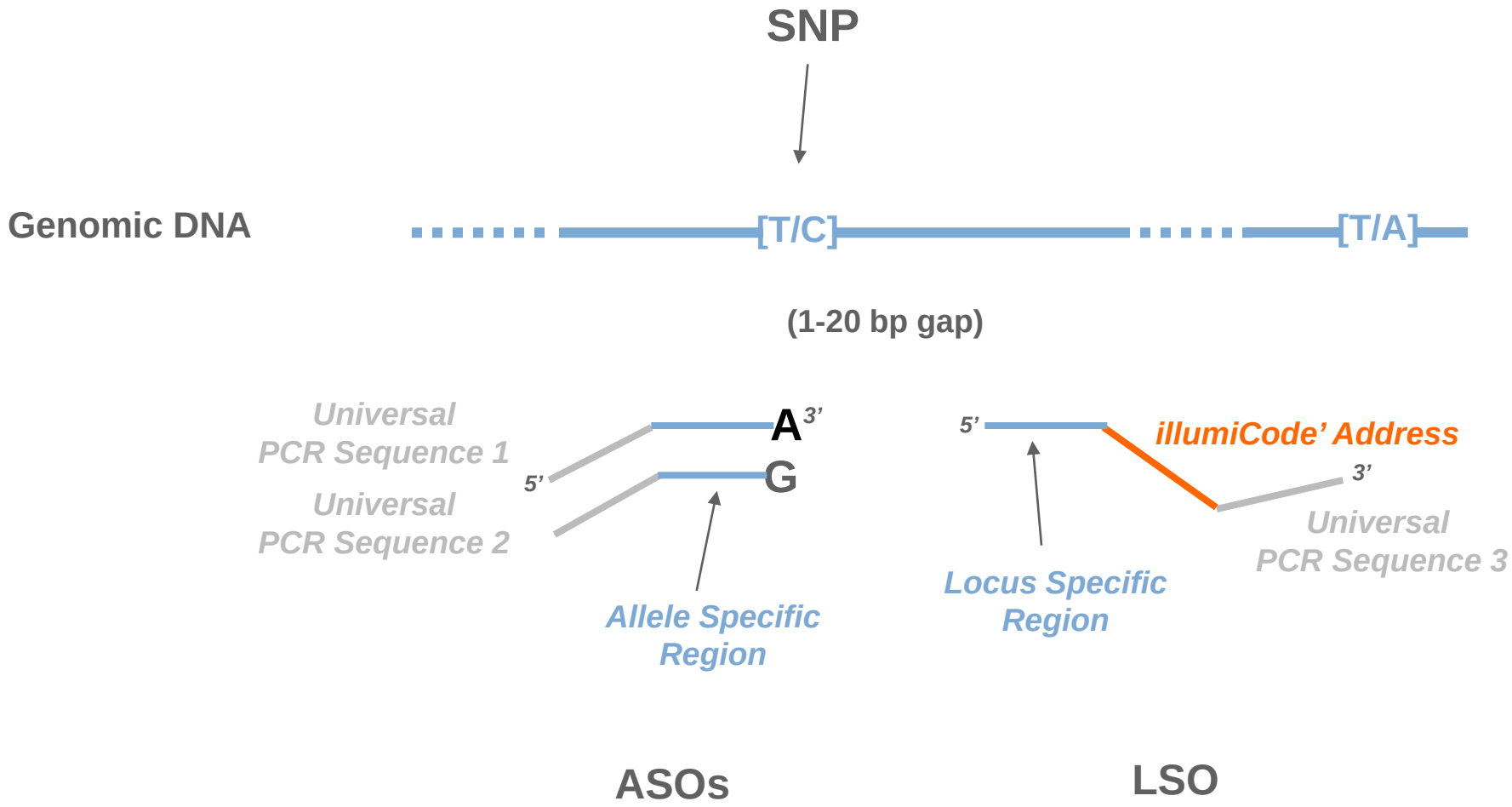
GoldenGate Assay Biochemistry

GoldenGate Assay: Primer Design

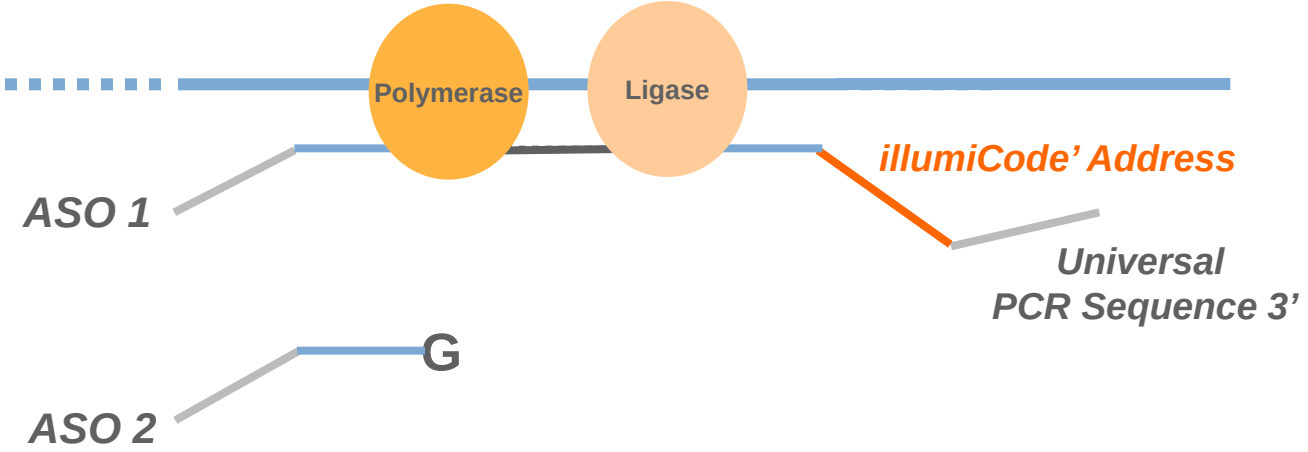


GoldenGate Assay: Biochemistry/Assay Diagram

- Allele-specific extension and ligation

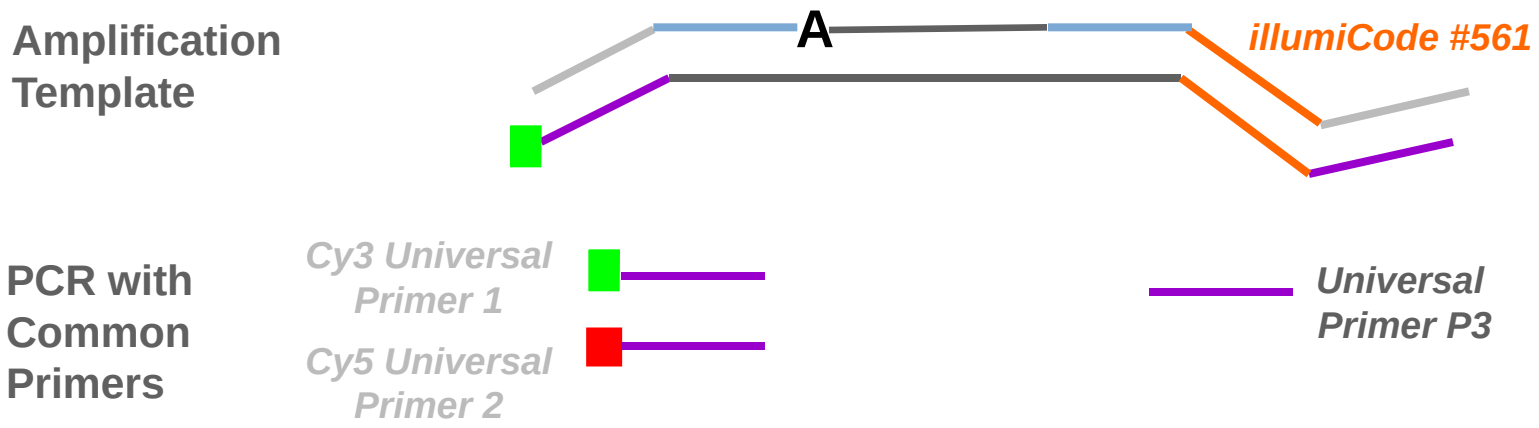
Genomic DNA

Allele Specific Extension & Ligation



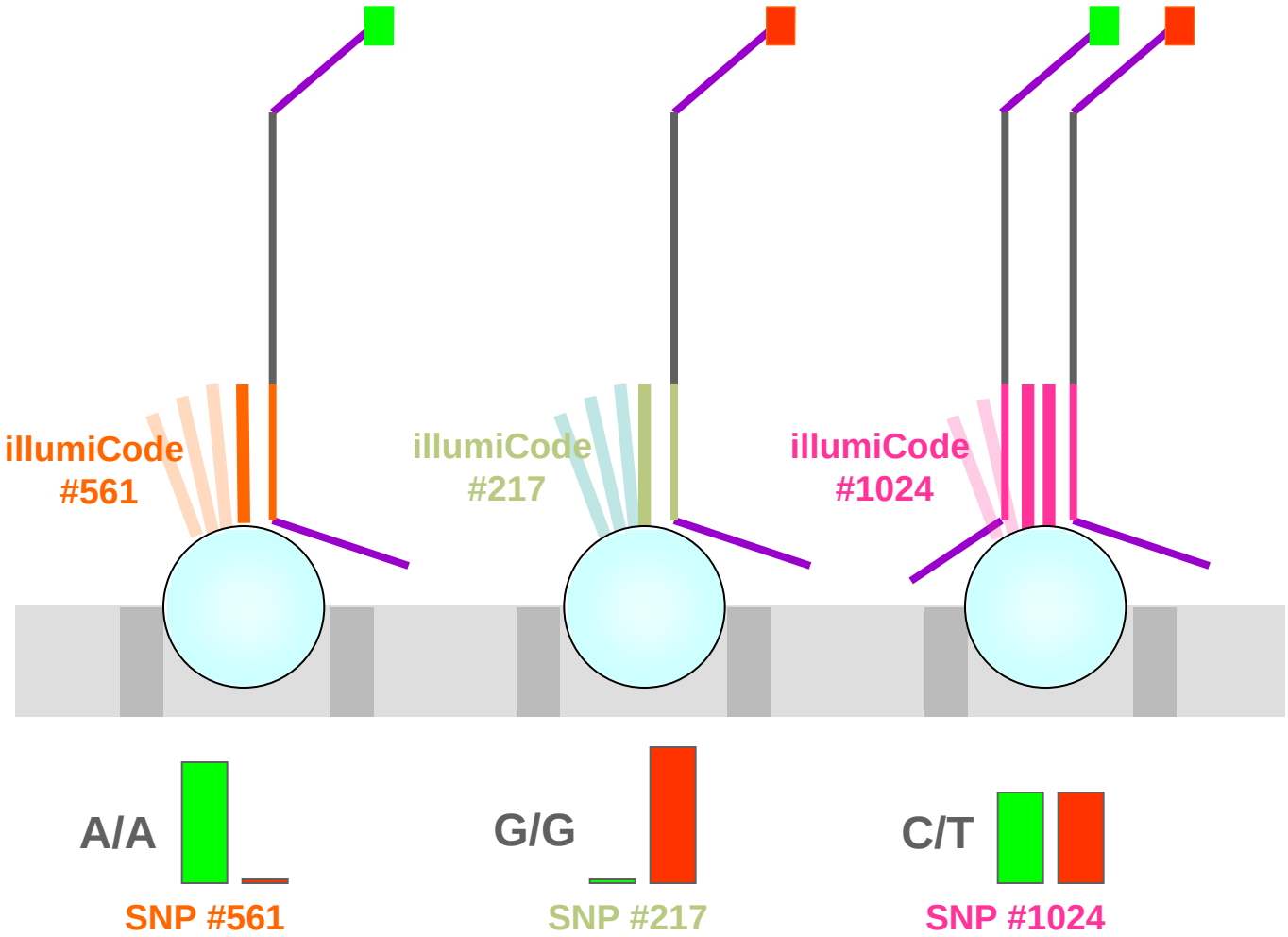
GoldenGate Assay: Biochemistry/Assay Diagram

- Amplification



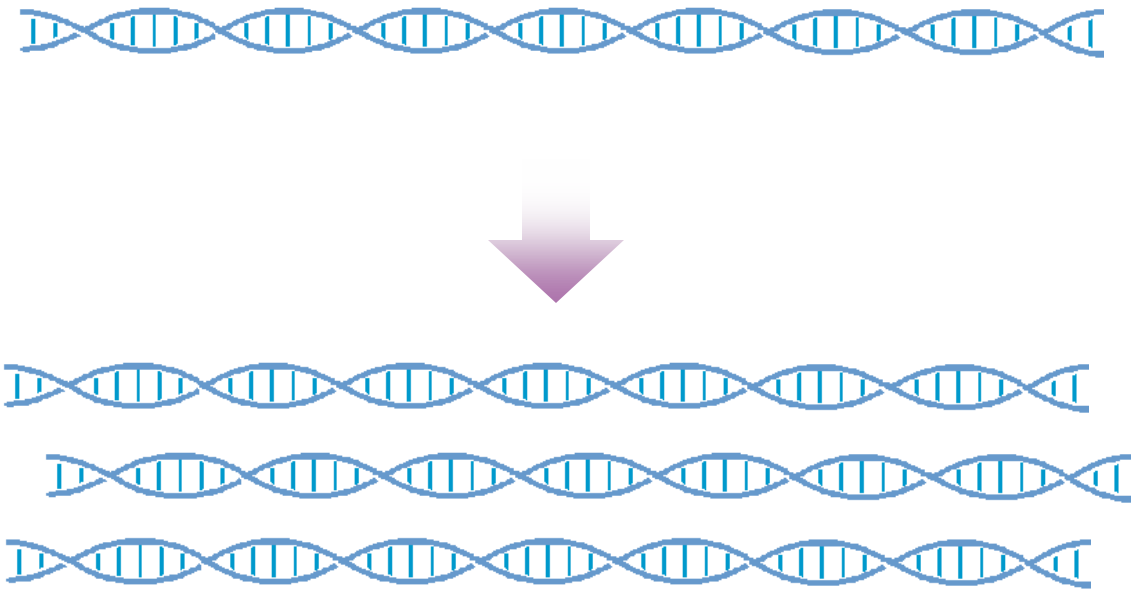
GoldenGate Assay: Biochemistry/Assay Diagram

- Hybridization to VBP



Infinium Assay Biochemistry

Whole-genome amplification



- Optimized WGA reaction minimizes GC bias
- Up to 1000-fold amplification

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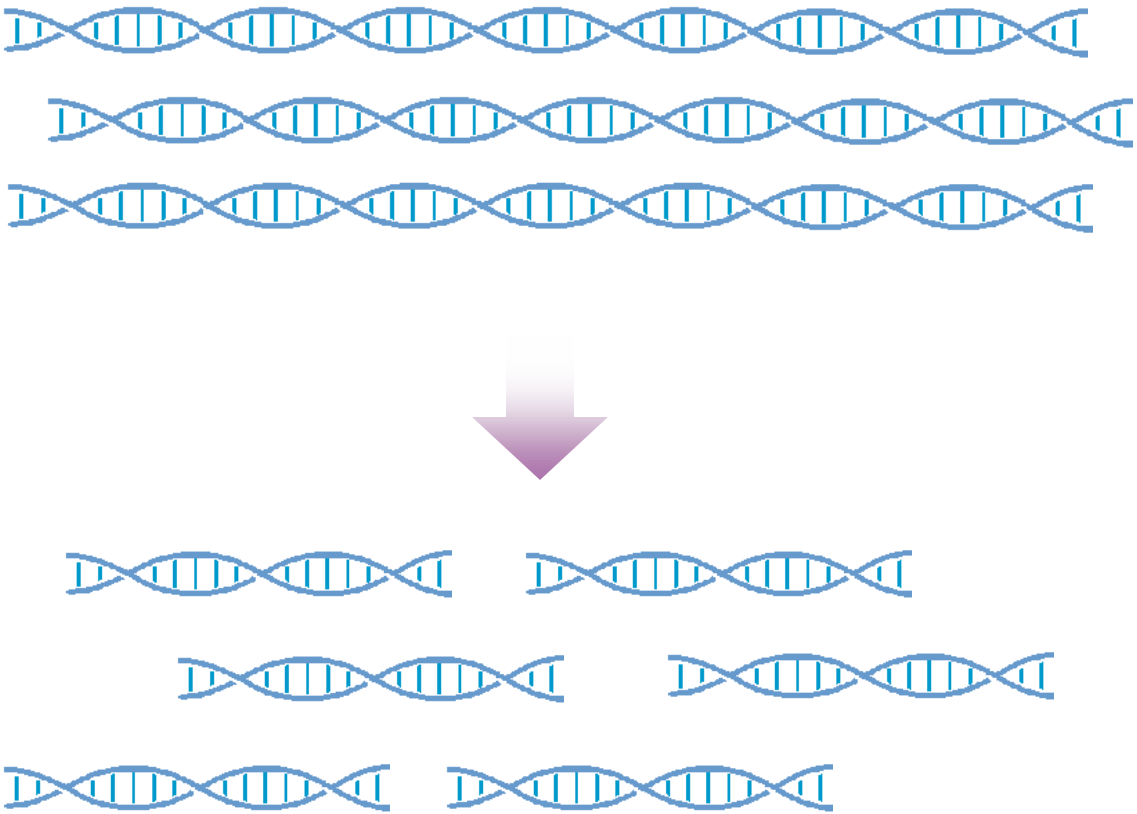
Fragmentation



- Robust endpoint fragmentation
- Allows access to vast majority of genome

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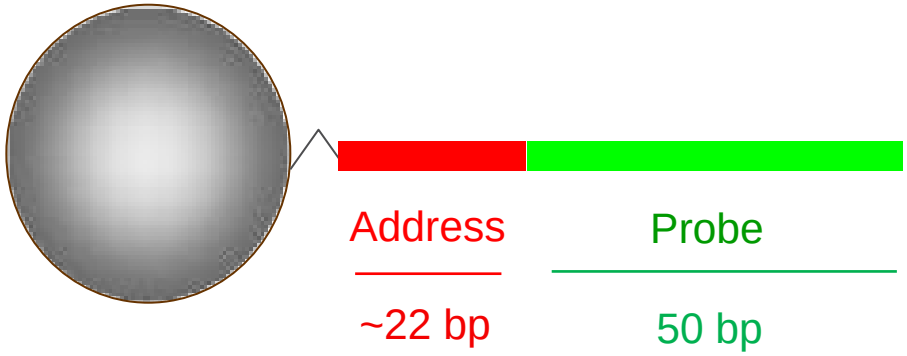
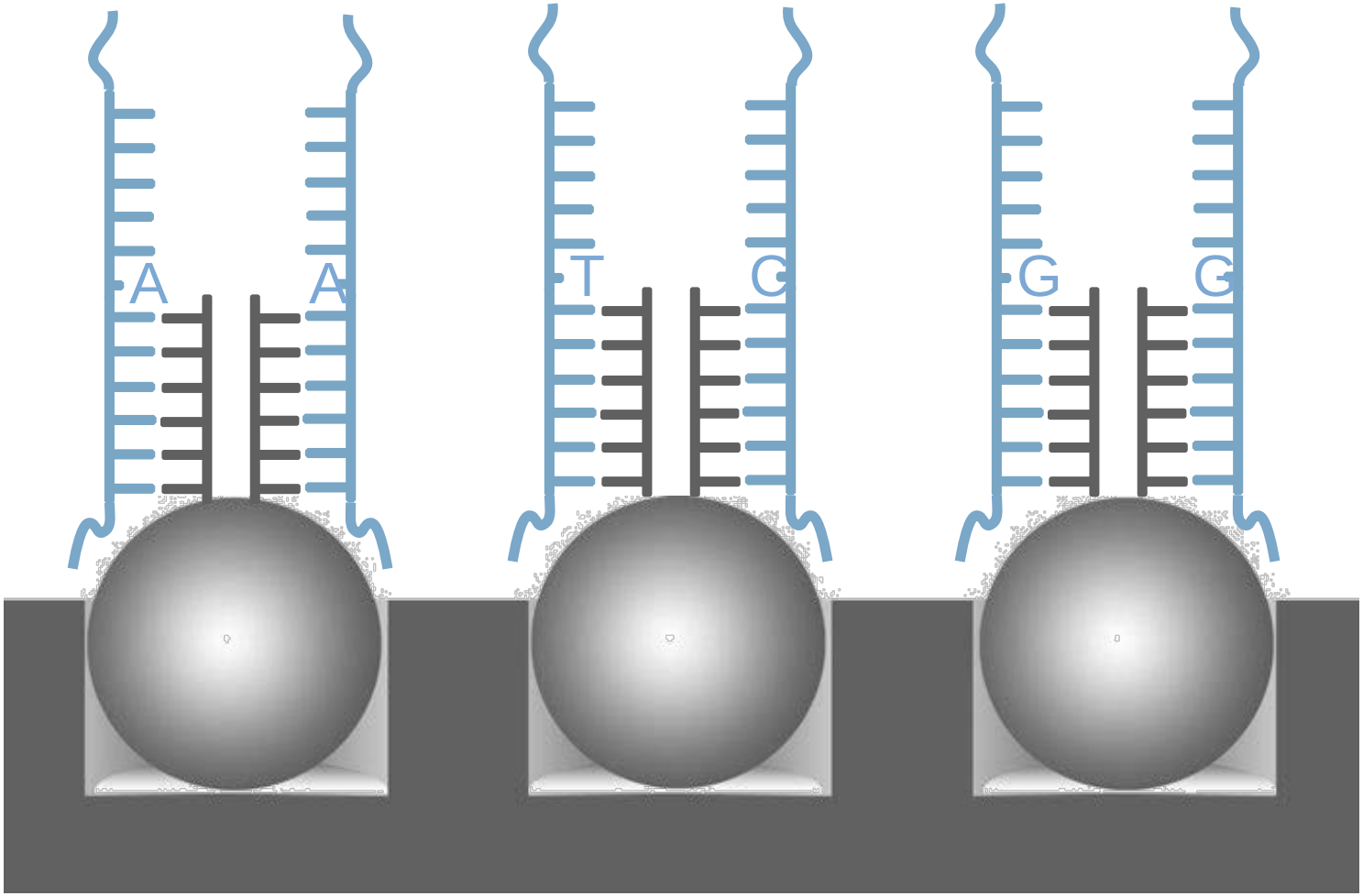
Infinium Probes and BeadTypes

Locus-Specific



Hybridization



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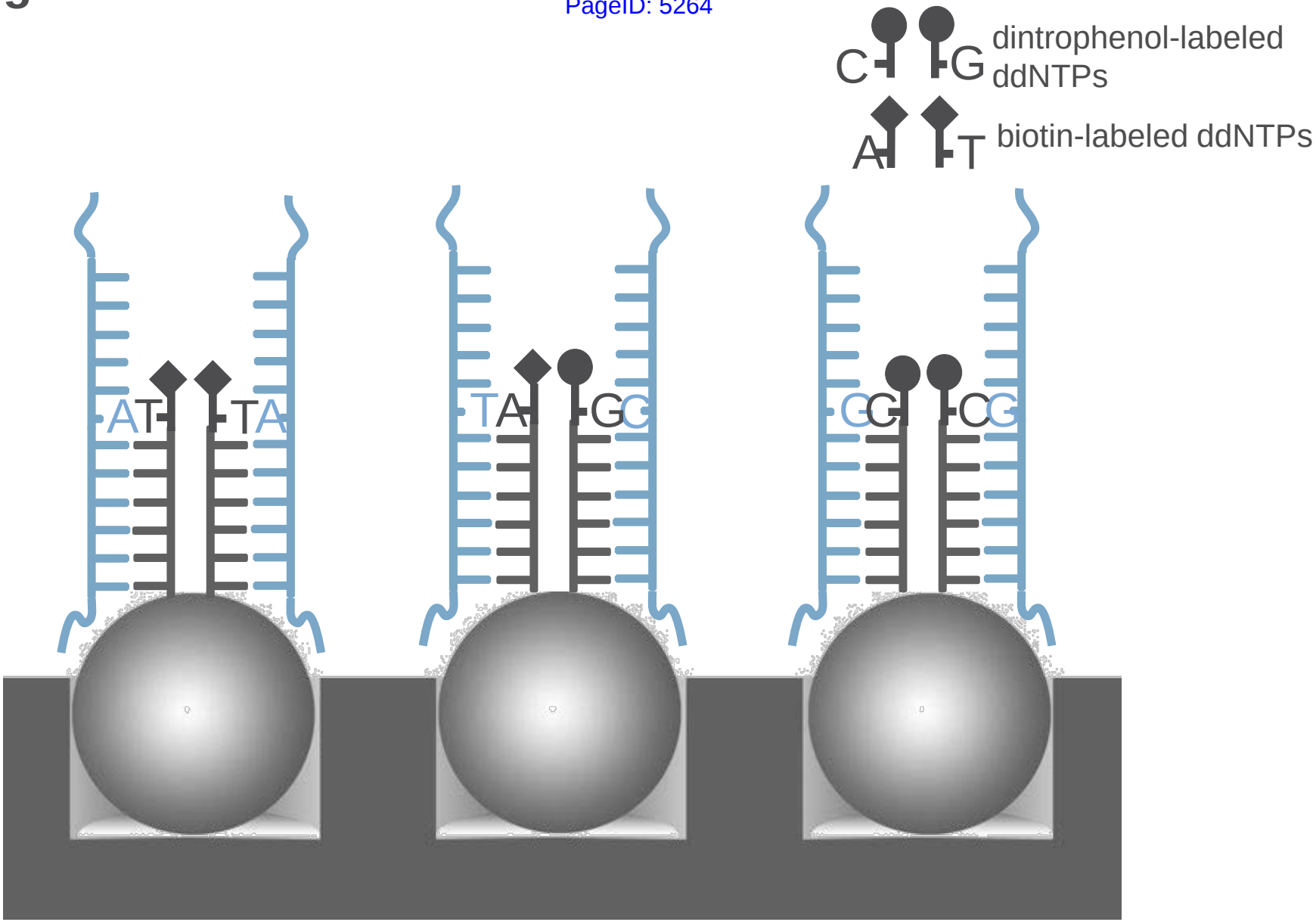
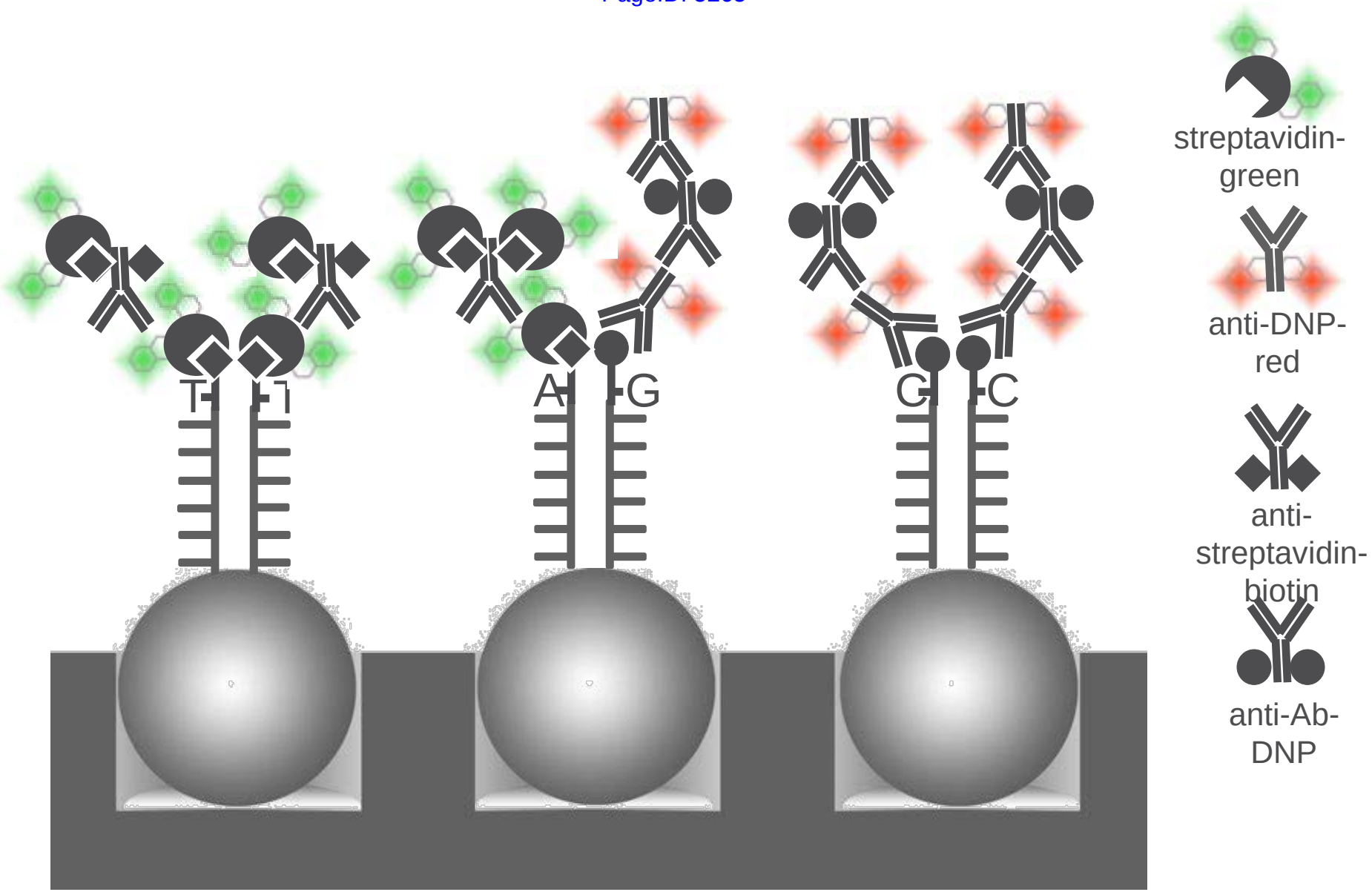
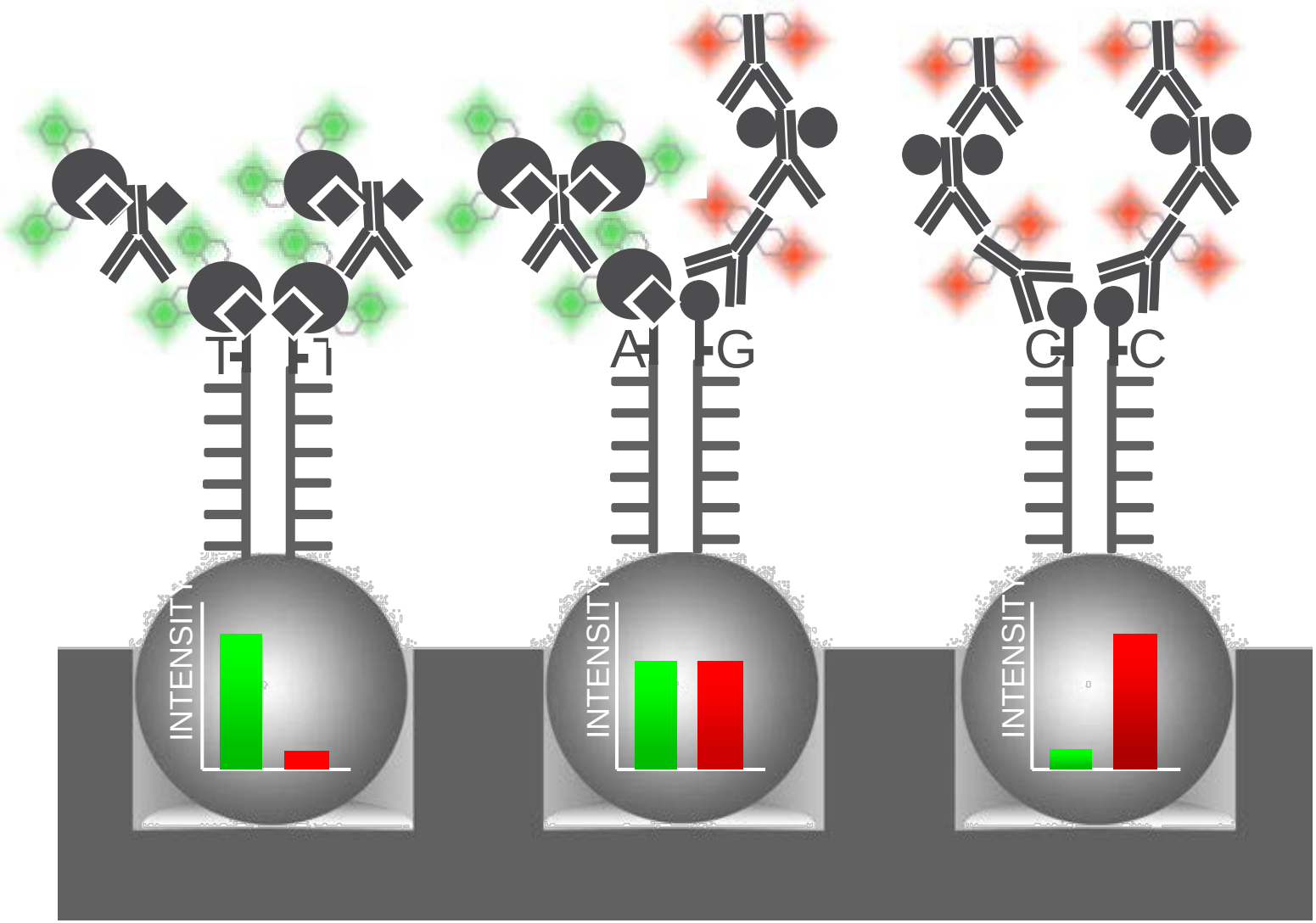
Single Base Extension




T
T
A
G
G
C
streptavidin-green
anti-DNP-red
anti-streptavidin-biotin
anti-Ab-DNP


T
T
A
G
G
C
INTENSITY
INTENSITY
INTENSITY

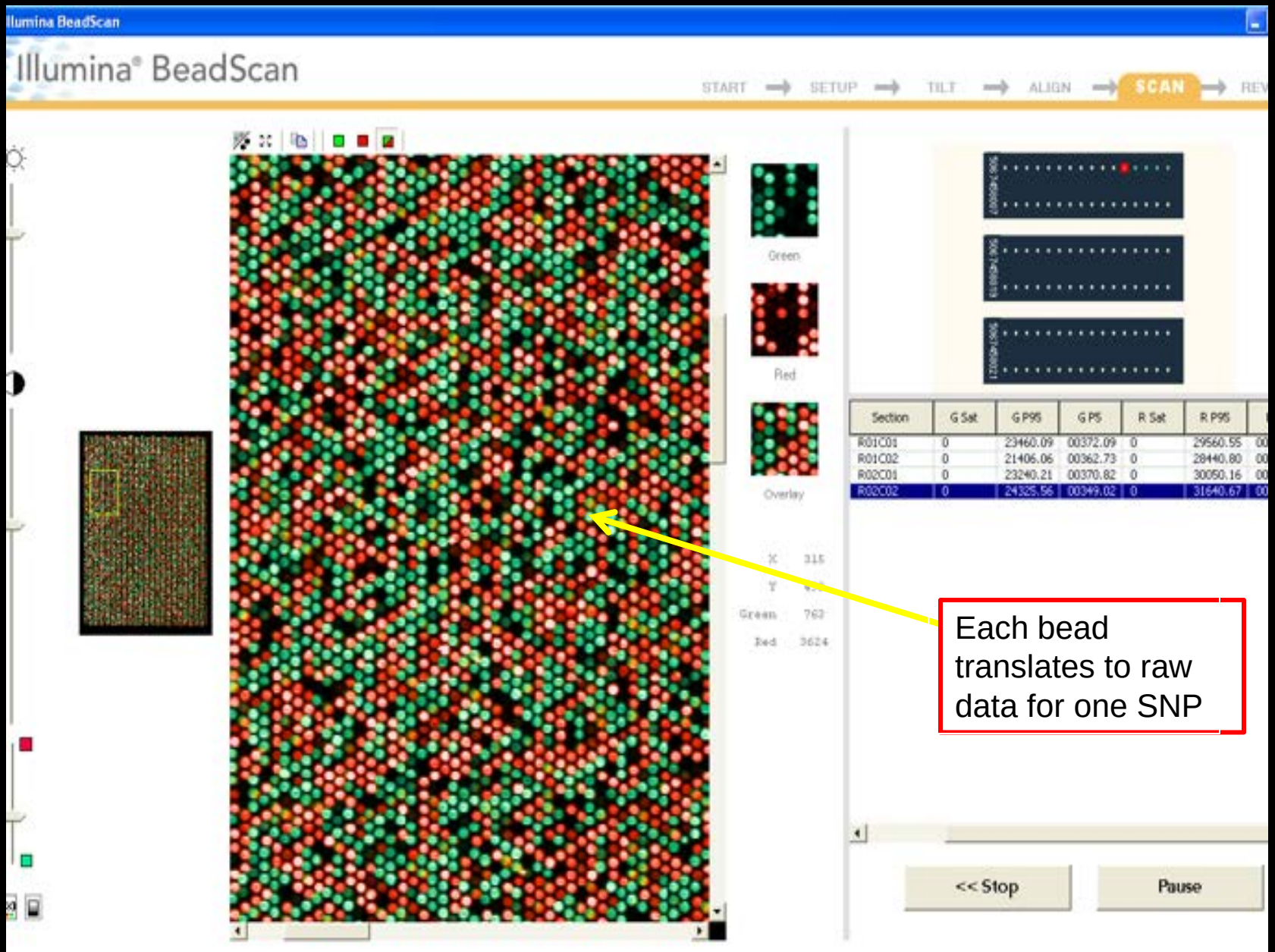
BeadChip Scanning and SNP Assay Detection

- Input file – .dmap files containing bead locations
- Output file – .idat files containing hybridization intensity data

BeadStation

To scan BeadChips and generate raw data

BeadChip scanning in progress



Data Analysis and Genotype Calling using GenomeStudio Software

Loading Data

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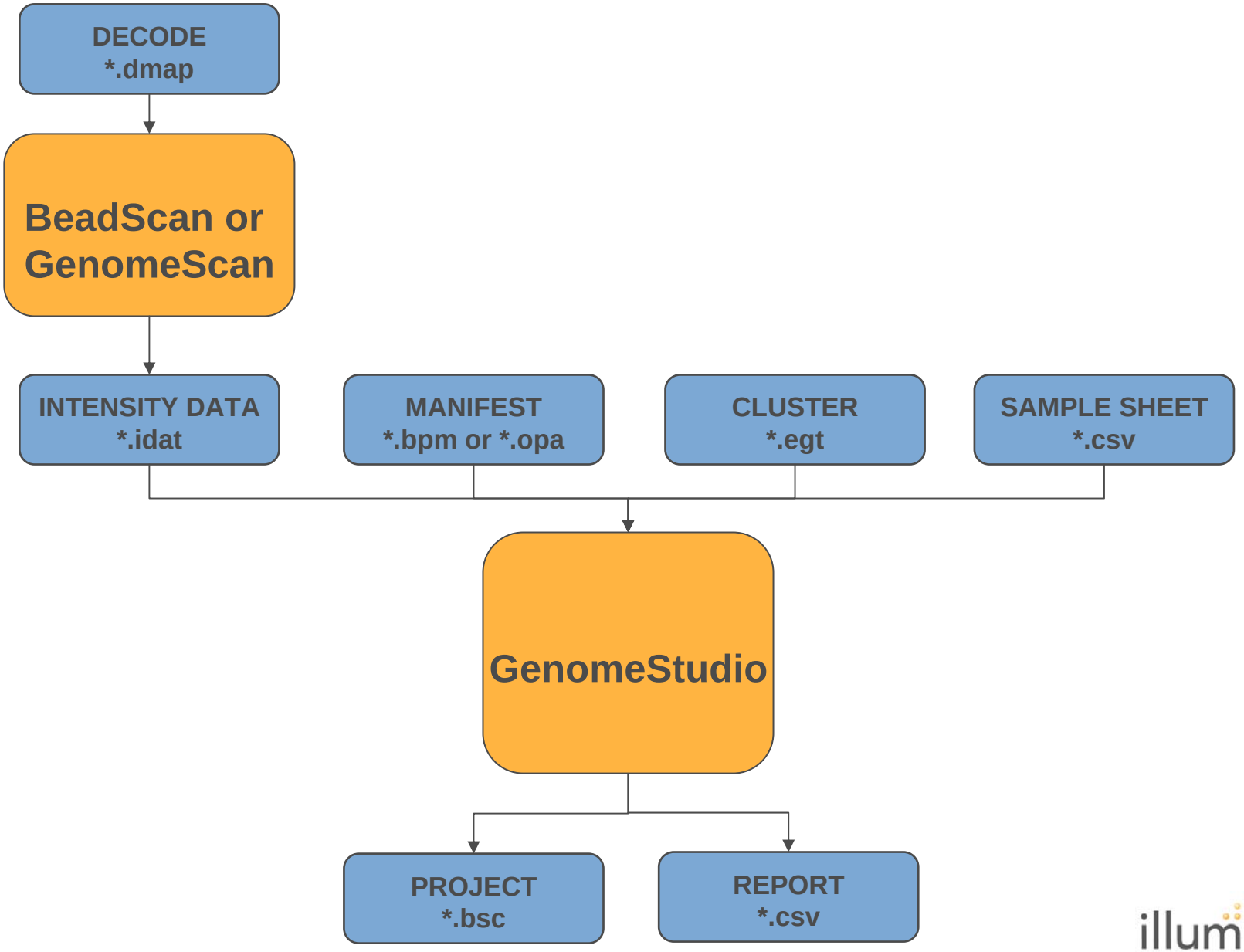
File Types


DECODE
*.dmap
BeadScan or GenomeScan
INTENSITY DATA
*.idat
MANIFEST
*.bpm or *.opa
CLUSTER
*.egt
SAMPLE SHEET
*.csv
GenomeStudio
PROJECT
*.bsc
REPORT
*.csv

Load Data

File	Extension	Description	Source	Required?
Data	*.idat	Contains the mean red and green signal intensities for each bead type	GenomeScan	Yes
Manifest	*.bpm *.opa	Lists the SNP ID and annotation for each bead type	iCom	Yes
Cluster	*.egt	For each locus, defines the allowable signal intensity ranges for AA, AB, and BB genotypes	iCom / User-created	No
Sample Sheet	*.csv	For each sample, lists the microtiter plate locations, replicate and family relationship information	User-created	No

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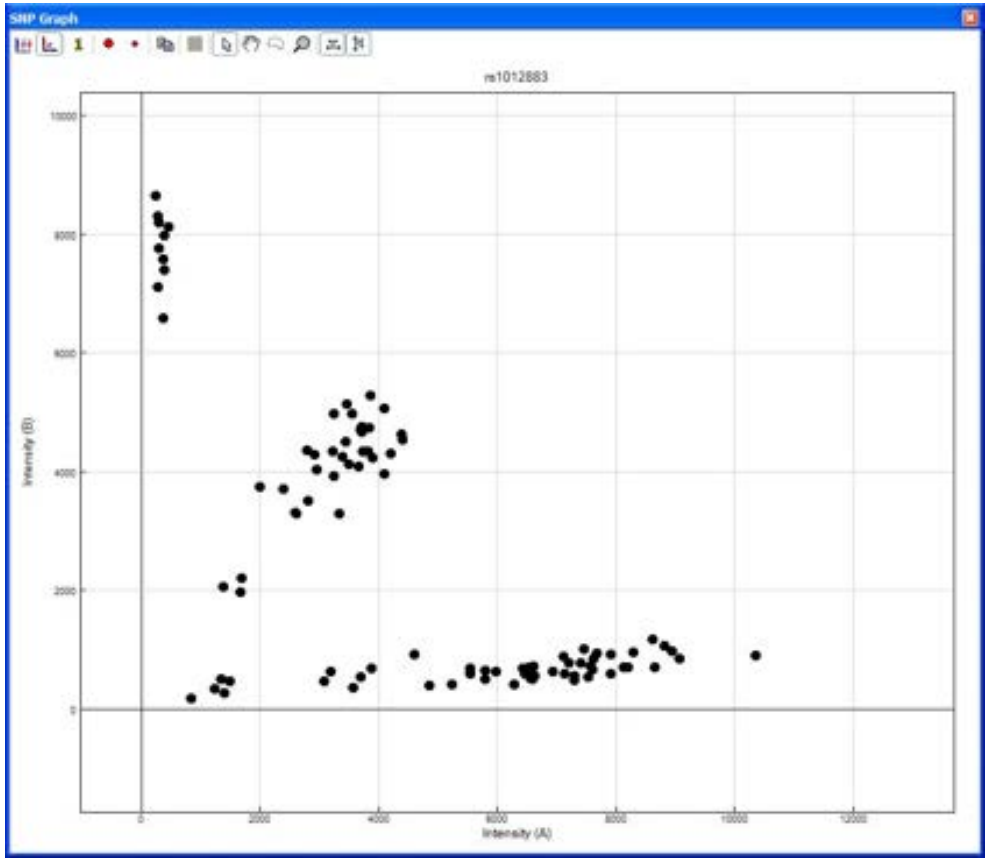
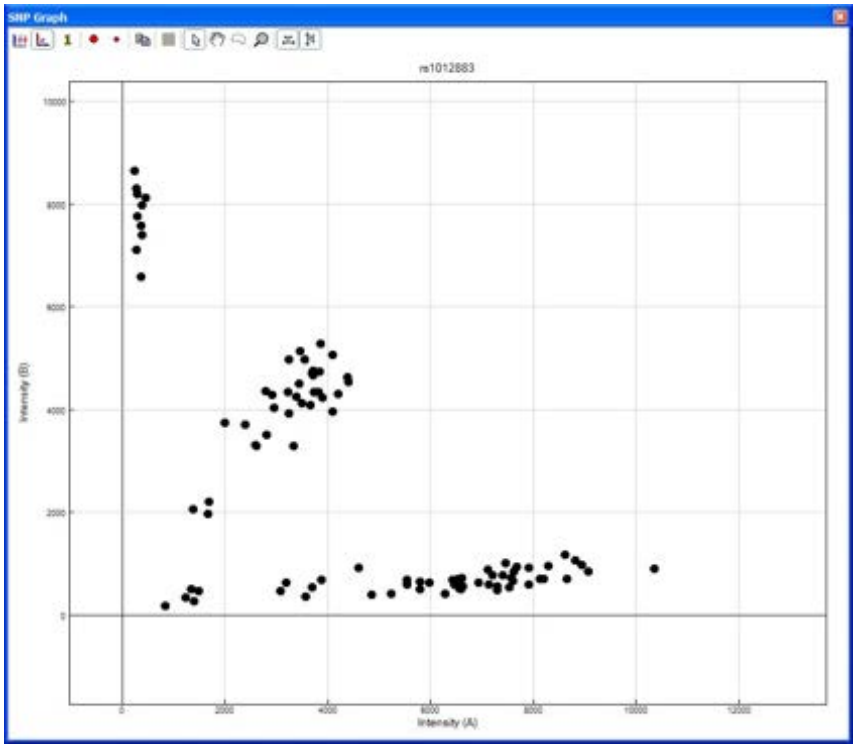
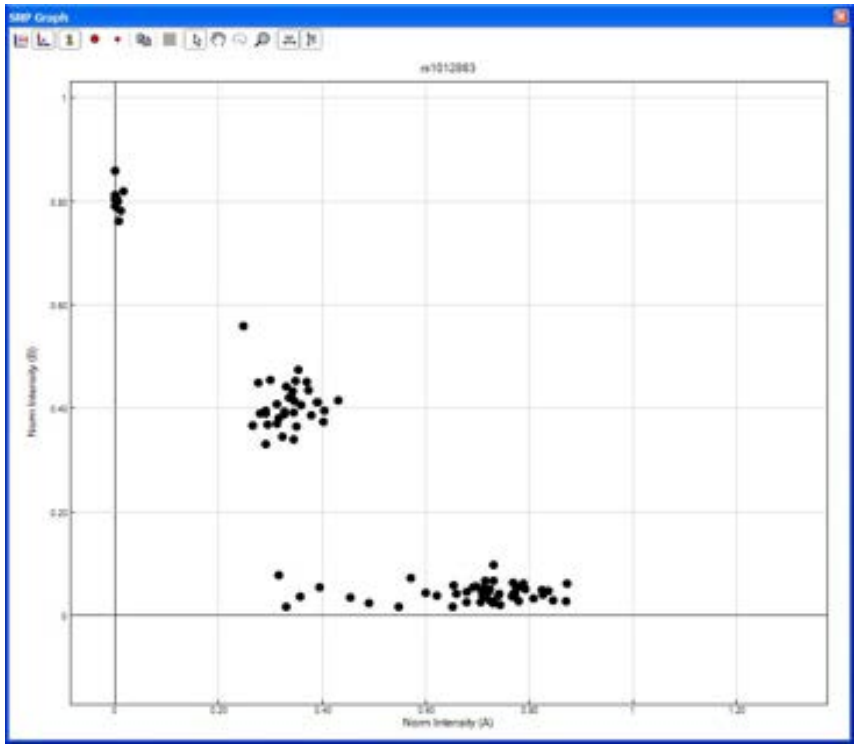
Plotting intensities in Cartesian space



Signal intensities for 96 samples at one locus
Y axis is green signal intensity
X axis is red signal intensity

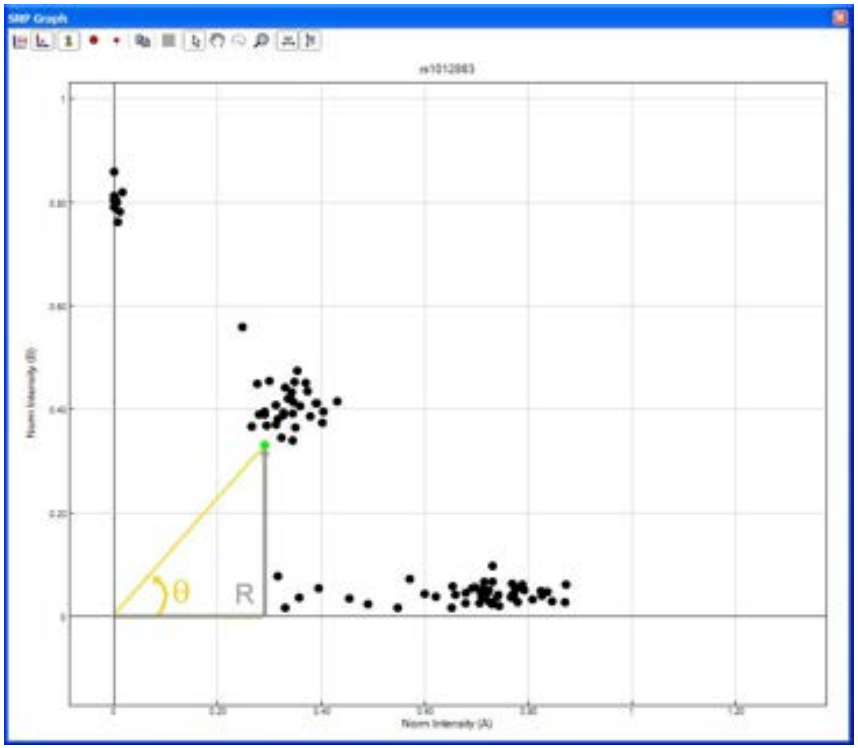
Normalization

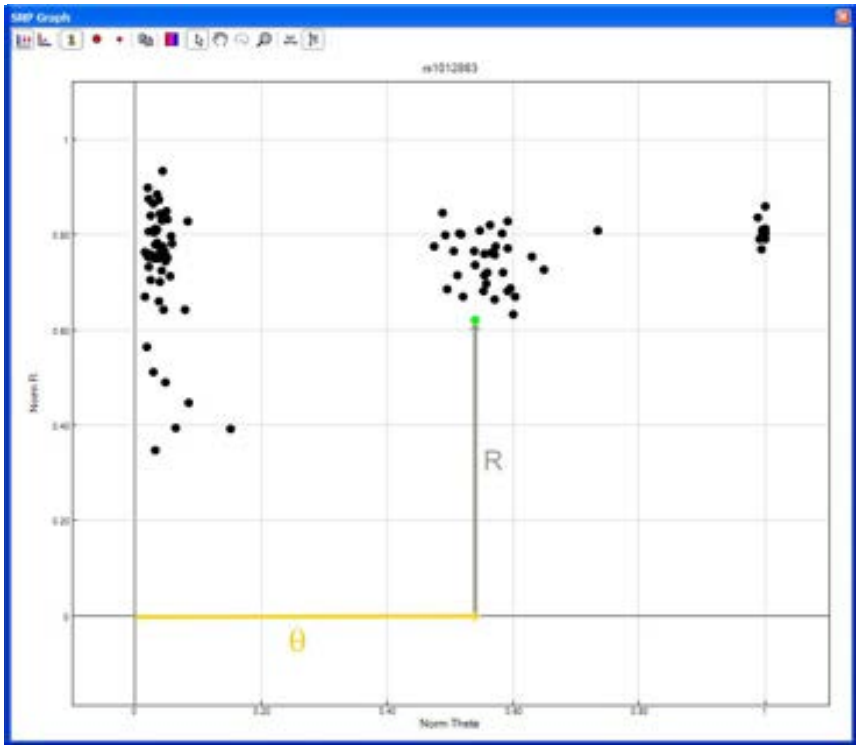




Proprietary normalization algorithm

SNP Graph - Polar Coordinates

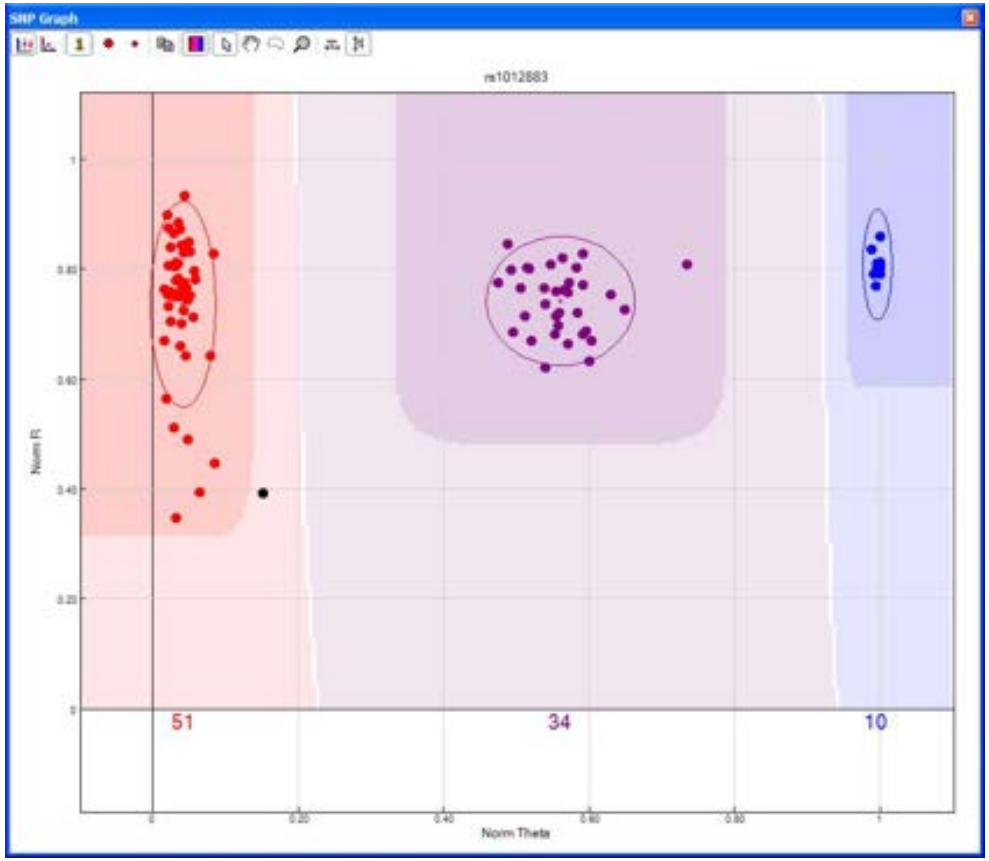




Θ = angle from X axis

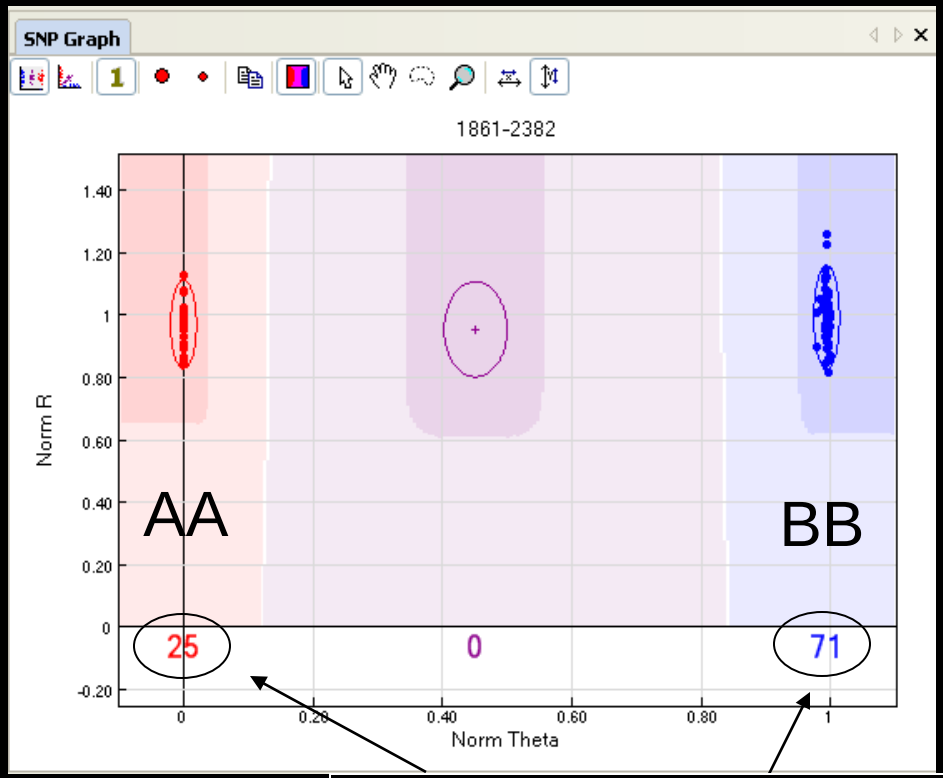
R = A + B

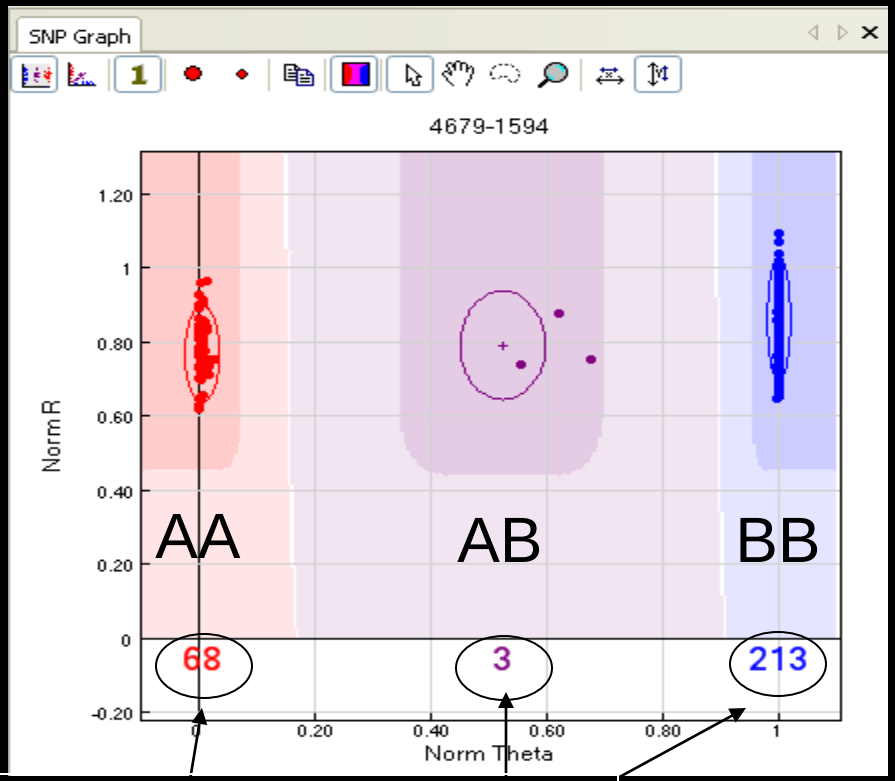
Clustering



- GenCall score reflects the distance of a data point to the centroid of a cluster
- GenCall score is a representation of the confidence with which a genotype call is made (GenTrain score and data to model fit)
- Dark shaded regions are call regions (GenCall score > 0.25 for GoldenGate and 0.15 for Infinium)

An Example of Barley SNP Genotype Calls





Number of individuals with that genotype

Genotype Data Report

[Header]

GSGT Version	1.6.3
Processing Date	3/19/2010 11:36
Content	GS0007511-OPA.opa
Num SNPs	1536
Total SNPs	1536
Num Samples	96
Total Samples	96

[Data]

SNP	09OR-01	09OR-09	09OR-17	09OR-25	09OR-33	09OR-41	09OR-49	09OR-57	09OR-65	09OR-73	09OR-81	09OR-89	09OR-02
1375-2534	BB	BB	BB	BB	BB	BB	BB	BB	AA	BB	AA	AA	BB
5019-879	AA	AA	AA	AA	AA	AA	AA	AA	BB	BB	BB	BB	AA
5764-430	AA	AA	AA	AA	AA	AA	AA	AA	BB	AA	BB	BB	AA
5128-1831	AA	AA	AA	AA	BB	AA	AA	AB	AA	AA	AA	AA	AA
3026-1011	BB	BB	BB	BB	BB	BB	BB	AA	AA	AA	BB	BB	BB
4407-1344	BB	BB	BB	BB	BB	AA	AB	BB	BB	BB	BB	BB	BB
6157-1233	AA	AA	AA	AA	AA	AA	AA	AA	AA	AA	AA	AA	AA
9251-852	AA	AA	AA	AA	AA	AA	AA	AA	AA	AA	AA	AA	AA
ABC11290-sfp44-06	BB	BB	AA	AB	AA	AA	AA	BB	AA	AA	AA	AA	BB
5893-1285	--	AA	BB	AA	BB	AA	AA	AA	AA	BB	BB	AB	BB
2477-377	AA	AA	AA	AA	AA	AA	AA	BB	BB	BB	BB	BB	AA
2208-279	AA	AA	AA	AA	AA	AA	AA	AA	AA	AA	AA	AA	AA
4434-804	BB	AA	BB	AA	AA	AA	AA	AA	AA	AA	AA	AA	AA
1294-473	BB	BB	BB	BB	BB	BB	BB	BB	BB	BB	BB	BB	BB
ConsensusGBS0234-1	BB	BB	BB	BB	BB	BB	BB	BB	AA	BB	BB	BB	BB
1473-1115	AA	AA	AA	AA	BB	BB	AA	AA	AA	AA	AA	AA	AA
ConsensusGBS0446-1	AA	AA	AA	AA	AA	BB	AA	BB	BB	BB	BB	BB	AA
ABC01838-2-2-322	AA	BB	BB	AA	BB	BB	BB	AA	BB	BB	BB	BB	BB
3443-1234	BB	BB	BB	BB	BB	BB	BB	BB	BB	BB	BB	BB	BB
ABC08077-pHv131-02	AA	AA	BB	AB	BB	BB	BB	AA	BB	BB	BB	BB	AA
3390-205	AA	AA	AA	AA	AA	AA	AA	AA	AA	AA	AA	AA	AA
1198-537	AA	BB	AA	BB	BB	BB	BB	BB	AA	--	--	BB	AA
6460-355	BB	BB	BB	BB	BB	BB	BB	BB	BB	BB	BB	BB	BB
2067-775	AA	AA	BB	AA	BB	BB	AA	AA	AA	BB	BB	AA	AA
2055-947	AA	AA	AA	AA	AA	AA	AA	AA	BB	AA	AA	AA	AA
2802-685	BB	BB	BB	BB	BB	BB	BB	BB	BB	BB	BB	BB	BB
3506-668	BB	BB	BB	BB	BB	BB	BB	BB	BB	BB	BB	BB	BB

Subject Private: Speak with Matthew?

From Francis Barany <barany@med.cornell.edu>

To: Valerie Cross <vlc1@cornell.edu>, Pearson, Matthew <mpearson@akingump.com>

Cc: Monib Zirvi <matzirvi@yahoo.com>, Francis Barany <barany@med.cornell.edu>

Date Mar 14, 2017 at 9:45 AM

Dear Valerie,

Hope you are enjoying the blizzard of 2017.

Monib and I would like to speak to Matthew about the IPR, before the upcoming 2nd deposition of Tyagi (this coming Monday).

Further, do you have answers to our questions on zip codes and software?

We are available on Friday, let us know if you would like to join the conversation.

Best,

Francis

[redacted]
barany@med.cornell.edu

[redacted]

Subject Re: Private: Speak with Matthew?

From Valerie Cross Dorn <vlc1@cornell.edu>

To: Francis Barany <barany@med.cornell.edu>

Cc: Matt Pearson <mpearson@akingump.com>, Monib Zirvi <matzirvi@yahoo.com>

Date Mar 14, 2017 at 11:09 AM

According to the news you avoided the worst of the storm and it is coming directly my way! I am working on a response to your questions, and have contacted Matt regarding your request to speak with him. Are you proposing that call to take place on Friday at 11? Please confirm. Valerie

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>
> Francis
>
> [redacted]
> [redacted]
> barany@med.cornell.edu
>
> [redacted]

View less

Subject Re: Private: Speak with Matthew, Friday, March 17th @ 11:00 AM

From Francis Barany <barany@med.cornell.edu>

To: Valerie Cross <vlc1@cornell.edu>, Matt Pearson <mpearson@akingump.com>

Cc: Monib Zirvi <matzirvi@yahoo.com>, Francis Barany <barany@med.cornell.edu>

Date Mar 14, 2017 at 11:25 AM

Dear Valerie and Matthew,

Sorry about the snow coming your way.

Thank you for working on a response to our questions. Meanwhile, Brian had suggested Monib and I re-look at the Markman wording and show how our patents cover Illumina products even with the ruling as it stands now. So we are diligently working on that.

Yes, we were thinking Friday, March 17th @ 11:00 AM — and will set it up if that time works for both you and Matthew.

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Francis

[redacted]
barany@med.cornell.edu

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> Francis
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> barany@med.cornell.edu
>
> [redacted]

View less

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From Francis Barany <barany@med.cornell.edu>

To: Matt Pearson <mpearson@akingump.com>

Cc: Monib Zirvi <matzirvi@yahoo.com>, Valerie Cross <vlc1@cornell.edu>, Francis Barany <barany@med.cornell.edu>

Date Mar 15, 2017 at 8:53 AM

Dear Matthew,

Would you please let me know your availability for a webex on Friday, March 17th @ 11:00 AM?

Valerie is able to join at that time, so let me know and I will set it up.

Best,

Francis

[redacted]

barany@med.cornell.edu

[redacted]

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[redacted]

View less

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To: Francis Barany <barany@med.cornell.edu>

Cc: Matt Pearson <mpearson@akingump.com>, Monib Zirvi <matzirvi@yahoo.com>

Date Mar 15, 2017 at 1:00 PM

Yes Francis, Matt and I are both available to participate in the call at 11 a.m. on Friday. I am not sure we need a web ex, but defer to you on whether you need documents to address Tyagi deposition issues with Matt. Valerie

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Francis

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

View less

Subject Re: WebEx meeting Friday @ 11:00 AM: Cornell - Pearson - Cross Dorn

From Francis Barany <barany@med.cornell.edu>

To: Pearson, Matthew <mpearson@AKINGUMP.com>, Valerie Cross <vlc1@cornell.edu>

Cc: Monib Zirvi <matzirvi@yahoo.com>, Francis Barany <barany@med.cornell.edu>

Date Mar 16, 2017 at 3:30 PM

Dear Matthew and Valerie,

Looking forward to our discussion tomorrow @ 11:00 AM

Matthew, thought you would appreciate the meeting password.

Best,

Francis

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

Begin forwarded message:

From: Francis Barany <messenger@webex.com>
Subject: (Forward to others) WebEx meeting invitation: Cornell - Pearson - Cross Dorn
Date: March 16, 2017 at 3:26:27 PM EDT
To: <barany@med.cornell.edu>
Reply-To: <barany@med.cornell.edu>

You can forward this invitation to others.
Hello,

Francis Barany invites you to join this WebEx meeting.

Cornell - Pearson - Cross Dorn
Friday, March 17, 2017
11:00 am | Eastern Daylight Time (New York, GMT-04:00) | 1 hr
Meeting number (access code): [redacted]
Meeting password: [redacted]

Add to Calendar

When it's time, join the meeting.

Join by phone

[redacted] Call-in toll number (US/Canada)

Global call-in numbers

Can't join the meeting?

IMPORTANT NOTICE: Please note that this WebEx service allows audio and other information sent during the session to be recorded, which may be discoverable in a legal matter. By joining this session, you automatically consent to such recordings. If you do not consent to being recorded, discuss your concerns with the host or do not join the session.

Subject Chee Abstract

From Monib Zirvi <matzirvi@yahoo.com>

To: <barany@med.cornell.edu>

Cc: Valerie Cross Dorn <vlc1@cornell.edu>, <sean.boyle@thermofisher.com>, <roger.chin@lw.com>, <Rip.Finst@thermofisher.com>, <mpearson@akingump.com>, <barany@med.cornell.edu>, <Doug.Lumish@lw.com>, <bjk44@cornell.edu>

Date Mar 18, 2017 at 11:26 AM

Two abstracts from the same meeting describing the same technology. Hybridization-based decoding is called universal ZipCode Array by Chee and JB Fan.

Mark Chee
Illumina, Inc.

Randomly Self-Assembled Bead-Based Arrays for Gene Expression Analysis

Mark Chee, Tim McDaniel, Shawn Baker, Semyon Kruglyak, Francisco Garcia, Kenneth Kuhn, Csilla Fenczik, Kevin Gunderson, and Jian-Bing Fan

Illumina, Inc., San Diego, CA

Self-assembled arrays of bead-based sensors have been developed. Each bead contains oligonucleotide probes that can hybridize with high specificity to complementary sequences in a complex nucleic acid mixture. The identity of each bead in the random array is determined by a hybridization-based decoding procedure. By formatting the miniaturized arrays into a matrix that matches a 96-well microtiter plate, many samples

can be processed efficiently in parallel. We are using this platform to develop assays in the areas of SNP genotyping, gene expression profiling, and protein

genotyping, gene expression profiling, and protein analysis. Progress in the area of gene expression profiling will be discussed.

Sent from my iPhone

On Mar 18, 2017, at 11:08 AM, Monib Zirvi <matzirvi@yahoo.com> wrote:

> Xiang-Dong Fu
>
> University of California, San Diego
> **Cancer Classification Based on MRNA Isoforms**
>
> *Xiang-Dong Fu[1], Joanne M. Yeakley[1], Jian-Bing Fan[2], Mark Chee[2], David Tarin[3], Michael Gribskov[4], and Michael Zhang[5]*
>
> *[1]Department of Cellular and Molecular Medicine, University of California, San Diego, [2]Illumina, Inc., San Diego,[3]UCSD Cancer Center, [4]San Diego Supercomputer Center, and [5]Cold Spring Harbor Laboratory*
>
> Recent completion of the human genome project has set the stage for understanding network regulation of gene expression in biology. One of the major surprises is the large number of mRNA isoforms generated by alternative splicing (60% of human genes express more than one transcript and this percentage is likely underestimated), which undoubtedly contributes to molecular diversity in complex biological pathways. In our battle against cancer, variations in mRNA isoforms may underlie many previously unrecognized mechanisms for cellular transformation, and therefore may prove valuable for cancer diagnosis and characterization of potential therapeutic targets.
>
> Our project aims at developing a genomic approach to alternative splicing because current techniques for assaying alternative splicing rely on low throughput methods that are not suitable for genome-wide analysis. The technology utilizes the

addressable zip- code strategy on fiber optic-based microarrays developed at Illumina. Briefly, DNA oligos are used to cover specific splice junction sequences and each isoform-sepcific oligo is linked to a unique zip-code sequence. The oligos are first hybridized to total RNA and those detecting specific alternative splicing events are selectively amplified by PCR. Individual splicing events are then sorted and quantified on a universal Zipcode array. Using this novel microarray technology, we can detect specific alternative splicing events with unprecedented specificity and sensitivity, reaching to the single cell level in certain cases. Furthermore, semi-quantitative data are obtained from a panel of experimental cell lines and 90% of data points match the results obtained by conventional RT-PCR. Although we have been focusing on technology development in the initial R21 phase, our research has already led to the discovery of a number of striking cell-specific alternative splicing events in our model systems.

In the future, we plan to refine the assay to determine optimal experimental conditions for large scale application of the technology. We are interested in coupling our technology with sample preparation methods, such as immunofractionation of cells and laser capture microscopy. This will allow us to analyze alternative splicing in cell populations associated with distinct cancer stages. In particular, we plan to examine several hundred prostate cancer samples available at the UCSD Cancer Center to explore the utility of variations in alternative splicing for cancer classification. Parallel to our experimental efforts, our collaborators on the team will develop computational tools to aid database construction and analysis.

Sent from my iPhone

Subject Privileged and Confidential: Source Code

From Francis Barany <barany@med.cornell.edu>

To: Pearson, Matthew <mpearson@akingump.com>, Valerie Cross <vlc1@cornell.edu>

Cc: Monib Zirvi <matzirvi@yahoo.com>, Francis Barany <barany@med.cornell.edu>

Date Mar 19, 2017 at 1:11 PM

Dear Matthew and Valerie,

Thank you for speaking with us on Friday. We will send out the revised deck with the new analysis of the claims using the "Markman wording" in a follow-up email.

Matthew, in our discussion, it appears that Illumina DID NOT REVEAL the SOURCE CODE to you FOR THEIR COMPUTER PROGRAMS used to generate their early zip code sequences, NOR THEIR DMAP DLL FILES SOURCE CODES. Also, when we asked about whether they released certain sequences, you said you had to "look at your notes".

We are thus re-sending you our comments/questions from February 20th below (updated a bit), which we believe are more relevant than ever, since we now know the dll files are required for at least some of Illumina's sequencing instruments as well. It is our view that Illumina had a systematic and willful program to try and hide their use of zipcode arrays, including using about a dozen other names, and that intensified after Illumina filed an Antitrust suit against ABI in 2004 (which we only learned about in the last two weeks).

We are not requesting you to reveal the sequences that are mentioned in the various

applications. Matthew, would you please look at your notes and go back over the documents/files submitted, to understand if Illumina provided to YOU

submitted, to understand if Illumina provided to YOU the full sequences for:

1. A set of 16 adapters Kevin Gunderson claims are "in use" in the Illumina provisional application 60/135,123 filed on May 20, 1999? Gunderson also claims an additional 100 will be prepared, do you have those?

2. A set of 128 unique "universal Zipcode array" addresses in the Illumina provisional application 60/180810, filed Feb. 7, 2000 with only Jian-Bing Fan as inventor?

Looking forward to speaking next week.

Best,

Francis & Monib

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

As you know, Illumina does not make addressable arrays. They make assembled arrays. The beads go into random places, and if you use an assembled array "as is" to try to identify SNPs or look at expression data, you will see a bunch of random red or green fluorescent spots, and it is impossible to interpret.

To interpret the data, one needs addressable arrays. There are two ways to make addressable arrays – you can put your zipcode oligos down at known locations in an X-Y coordinate, or you can use zipcodes to decode where randomly distributed oligos (i.e. on beads) have been placed, again in an X-dimension and in a Y-dimension. When using the second approach, one then needs a "cheat sheet" for each array you make, that tells you which bead is in which well, by giving the X coordinate and the Y coordinate (called the BeadMap). That is the DMAP file you refer to in your email.

This was the key moment in the Zebala case, when David Walt admitted that to decode the arrays you just needed to know two dimensions, the X-dimension and the Y-dimension (see enclosed revised deck). You will also notice part 5, the red box at the bottom that says "Name: string zipcode", and then beneath that "Xvalues" and "Yvalues".

It is mission critical for us to see the original programing code, also known as the "source code" for the original dll

files, for example in SQL, or C++, or Microsoft.net, or Java, or JavaScript, or other programing languages. That is different from the files Monib downloaded, or the DMAP files that are made for each separate Beadchip. By way of example, in our own patent listing about 4,000 zipcodes (initially published as WO2001079548), we wrote a program to make sure there wouldn't be cross-hybridization problems between a zipcode the sequence at the junction of another zipcode and target sequence (i.e. the composite oligo) – this was several hundred lines of code and took up 13 pages in a printout (enclosed, Fig. 35). As you can see, the original program often has comments that explain what is being done in the program.

Likewise, we strongly suspect – given that the compiled listing already links the words "zipcode" with "Xvalues" and "Yvalues" that the source code would clearly delineates exactly what is going on in the program.

The key reason this is important is because Illumina claims their arrays — including the infinium SNP & copynumber BeadChip, infinium methylation BeadChip, and expression BeadChip arrays — are not "zipcode" arrays.

We all know this is not true. WE believe a compelling argument can be made that Illumina's failure to release the original source code for the "Common Verascan.dll", and "Illumina datafiles.dll" files (and additional programs as detailed below) was to HIDE their own admission that all their arrays are really zipcode arrays, and this constitutes willful concealment of material facts.

Now it is time for Judge Stark to know in no uncertain terms that Illumina has mislead him, that the Illumina Infinium BeadChips and all other Illumina array products are all zipcode arrays.

Furthermore…

We only recently uncovered that in Illumina's initial submition of provisional application 60/227,948 (M. Chee and K. Gunderson) on August 25, 2000, they called our zip codes as "IllumaCodes". In Illumina's full application 09/940,185 filed on August 27, 2001 (K. Gunderson & M. Chee), they renamed them as "Seq. ID No.", and further, only provided the sequence information as scanned tables. The USPTO wrote a letter to Illumina on October 19, 2001 stating that applicants must provide an initial computer readable form (CRF) copy. Illumina obviously tried to limit the USPTO's ability to search the sequences, despite the fact they were clearly generated on a computer.

Since the GoldenGate assay, and other Illumina publication refer to our zip codes as "IllumiCode" (trademarked) array, and the individual addresses as "illumiCodes" (i.e. illumiCode # 561, #217, #1024), it would not be unreasonable to hypothesize that there is some overlap between the list of "IllumaCodes" and "illumiCodes".

(Put another way, the probability of randomly choosing two names where 9 of 10 letters match in order is 26 to the 9th power, which is 1 in 5.4 trillion, or to put it in DNA language, there would be substantial cross-hybridization!).

Adding to this, in the First Amendment to the Joint Development Agreement, signed by John R. Stuelpnagel and dated March 27, 2001 (in other words before the August 27, 2001 submission), there is a call for defining and developing "Tag Sequences for the Collaboration Product", which we all now know are just another name for zipcode sequences.

All such sequences are covered by the '917 family of patents. This leads us to the following questions:

1. Did Illumina provide the SOURCE CODES for the "Common Verascan.dll", and "Illumina datafiles.dll" files – both of which contain the word "zipcode" -- to Akin Gump?

2. Did Illumina provide the SOURCE CODES for the software they wrote to generate the initial "IllumaCodes", and all subsequent revisions to Akin Gump? Do these programs contain the word "zipcode"?

3. Did the SOURCE CODES for the software they wrote to generate the initial "IllumaCodes" contain the initial 16 zipcodes from Barany's original unpublished 465 list, or did they add them afterwards to the tables in their US20030096239 patent application?

4. Did the SOURCE CODES for the software they wrote to generate the initial "IllumaCodes" contain a subroutine to check a new probe sequences against all previous decoder sequences for complementarity scores of < 14 (less than 14) of which there are 1,461 pairs that do not follow that rule in the 4,000 "IllumaCodes" listed in table 1, or did the source code use the term "<= 18" (less than or equal to, which is exactly what Barany taught)?

5. Did Illumina provide the SOURCE CODES for the "Tag Sequences for the Collaboration Product", and all subsequent revisions to Akin Gump? Do these programs contain the word "zipcode"?

6. Did Illumina provide the SOURCE CODES for the software they wrote to generate the current set of "IllumiCodes" or whatever they are calling the zipcodes on their current "Illumina infinium humanmethylation450 beadchip" "llumina Infinium HD BeadChip", "Sentrix Universal Array Matrix", "Illumina Human Whole-Genome DASL HT Assay", "HumanHT-12 v4 Expression BeadChip", or any other arrays sold by Illumina, and all subsequent revisions to Akin Gump? Do these programs contain the word "zipcode"?

7. Do you know which of Illumina's current and prior BeadChip products use our original 16 zip codes? The 60/172,106 Kevin Gunderson application as originally filed on Dec. 23, 1999? The 60/180810 provisional application, Filed Feb. 7, 2000 with Jian-Big Fan as the only inventor, that refers to universal BeadArrays with 128 unique addresses (zipcodes)?

If Illumina did not reveal the SOURCE CODE, i.e. original programing code, can we force them in court with a motion, such that we reveal their willful concealment of material facts?

Would this be grounds for appeal, if the SOURCE CODE was never revealed to Judge Stark and the Cornell legal team?

If Illumina did reveal the SOURCE CODE information, can we inform Judge Stark that Illumina themselves refer to the addresses on said infinium arrays as “zipcodes” contradicting their prior assertion that these are not zipcode arrays?

E. Claim Terms Related to Addressable Array-Specific Portions

The Claim Construction R&R recommends adopting Illumina's proposals for the claim terms "addressable array-specific portion," "address specific portion," and "zip code portion." (D.I. 449 at 40-44) Having reviewed the objections de novo, the Court OVERRULES Cornell's objections and ADOPTS the R&R with respect to these claim terms.

The R&R construed these terms to mean "portion of an oligonucleotide that selectively hybridizes to a complementary oligonucleotide located on an array, and does not hybridize to naturally occurring nucleic acids or to other oligonucleotides located on an array." (D.I. 449 at 43-44) Cornell objects to the requirement that the address array-specific portion binds to its complementary oligonucleotide on the array and to nothing else. But the claims themselves make clear that the addressable portion of a target oligonucleotide hybridizes to its complementary capture oligonucleotide. *See, e.g.*, '746 patent col. 61 ll. 62-67 (claim 1 reciting "contacting the sample . . . with the array . . . to hybridize the addressable array-specific portion of each target oligonucleotide to its complementary capture oligonucleotide."). The specification reinforces that the addressable portion is complementary to its capture oligonucleotide in order to enable hybridization. *See, e.g*, '917 patent col. 42 ll. 34-37.

Because the addressable array-specific portion must hybridize to its complementary capture oligonucleotide and, as discussed above, the capture oligonucleotides must differ from each other by 25%, the addressable array-specific portion will not hybridize to other oligonucleotides located on an array. (*See* D.I. 469 at 21) It is this selective hybridization that allows "addressable array-specific portions [to] guide each LDR product to a designated address on the solid support." Col. 42 ll. 25-26.

method, capture probes on microspheres bind to multiple locations on the target mRNA. Highly branched DNA labeled with biotin can then bind to the mRNA to form the sandwich. A streptavidin−phycoerythrin conjugate is then used to tag the bDNA, indicating the presence of the mRNA. This technique does not amplify or purify the target mRNA and can be used to analyze crude cell lysates or tissue homogenates. Flagella et al. multiplexed their assay to simultaneously detect 10 mRNA sequences with sensitivity down to 25 000 RNA transcripts.[229]

Several methods of SNP genotyping have also been demonstrated using suspension arrays. A direct hybridization technique was used by coating four types of fluorescently encoded microspheres with four oligonucleotides that varied by only a single base.[230] The labeled target then bound to only one of the four bead types identifying the SNP; eight SNPs have been detected in this way, requiring 32 bead types. Two other methods, known as oligonucleotide ligation assays (OLA)[231] and single base chain extension (SBCE) assays,[232,233] have also been used. Highly analogous to the GoldenGate and Infinium assays developed by Illumina Inc., OLA and SBCE use microspheres coated with oligonucleotides that act as address encoders, known as ZipCode, for binding amplified and labeled product. Unlike the Illumina encoding method, however, ZipCodes are not sufficient to identify the microsphere; instead, the microspheres are still fluorescently encoded, and the ZipCode acts as an intermediate linker to associate a particular bead with a particular SNP call. These methods have been used to identify over 50 SNPs simultaneously.[232] While fluorescently encoded suspension arrays are far below their planar array counterparts in terms of the number of SNPs they can call, they may fill a niche where a small number of SNPs need to be rapidly genotyped among a large number of samples.

4. Future Directions

There are many promising materials and technologies that one day may enable the preparation of very high density sensing arrays. In some cases, substrates have been created with feature sizes suitable for implementation with very high density sensing arrays. In other cases, functional materials containing both array characteristics and the ability to transduce signals exist. Other technologies exist that may one

Subject Privileged and Confidential: Cornell - Illumina Case Legal team only 1

From Francis Barany <barany@med.cornell.edu>

To: Roger.Chin@lw.com <Roger.Chin@lw.com>, Pearson, Matthew <mpearson@akingump.com>, Doug.Lumish@lw.com <Doug.Lumish@lw.com>, gregory.sobolski@lw.com <gregory.sobolski@lw.com>, Rip.Finst@thermofisher.com <Rip.Finst@thermofisher.com>, sean.boyle@thermofisher.com <sean.boyle@thermofisher.com>, Valerie Cross <vlc1@cornell.edu>, Brian Kelly <bjk44@cornell.edu>

Cc: Monib Zirvi <matzirvi@yahoo.com>, Francis Barany <barany@med.cornell.edu>

Date Mar 19, 2017 at 1:20 PM

Dear Roger, Matthew, Doug, Greg, Rip, Sean, Valerie, and Brian,

After our last phone meeting, we were instructed by Cornell to rethink the claims in view of the Markman language, just as Roger presented in his excellent summary slide decks.

Over the past two weeks, we have uncovered additional facts, as well as provided an updated interpretation of the claims in view of the Markman language. Both a primary and an appendix deck will be emailed to you in this and follow-up emails.

We understand that due to the protective order in the case there are certain facts we may not be privy to, and thus our views may be incomplete. John Zebala's entire Syntrix case was based on the doctrine of equivalence, yet he prevailed twice. Likewise, we feel that our position is currently significantly stronger than John's was before he

significantly stronger than John's was before he went to trial.

While I have had the pleasure of meeting both Rip and Matthew, I have not met Roger, Doug, Greg, or Sean in person. Hopefully, after this discussion, we will be able to schedule such an in-person meeting.

We are trained as scientists, and understand there are many legal issues that are not our field of expertise. However, we feel that we have been wronged, and we are confident that a jury will also agree with us.

It is not just that Illumina stole 16 out of our 4,633 zip codes. It is that Illumina stole them from an unpublished list at a time when they did not know how to get encoding and decoding to work. It is that Illumina used those very same zip codes to demonstrate the decoding. It is that Illumina must have secretly replicated our own work on a spotted array, exactly as taught in '917, otherwise, they would not know if their bead arrays were correct. It is that those 16 zip codes were so critical in the early years of their work, that Illumina renamed them as their first 16 IllumaCodes. It is that those 16 were critical for their quality control checks. It is that in all universal zip code arrays, pooled hybridization checks are necessary for quality control, prior to use. It is that Mark Chee and Jian-Bing Fan admitted that "hybridization-based decoding procedure" was incontrovertibly linked to "a universal Zipcode array". It is that Illumina conveniently allowed two key witnesses, Mark Chee and Jian-Bing Fan to escape to China to avoid depositions in the summer/fall or 2015.

It is that Illumina tried and failed to commercialize 7 other techniques to decode their arrays, and the final address encoders they used were zip codes. It is that Illumina used our teachings to create all subsequent zip codes, as derivatives of our original 16 zip codes. It is that Illumina willfully tried to deceive the USPTO, by sending only scanned tables, so the USPTO could not do sequence searches, and renaming them as "Seq. ID. No." instead of "IllumaCodes". It is that Illumina willfully tried to deceive investors and customers that they

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Thus, in reviewing the slides enclosed in the follow-up emails, in addition to wearing your legal hat, think if this happened to your brother, and what you would do to protect his rights.

In discussion with Valerie, she recommended a follow-up webex. Would you kindly let us know your availability for a webex meeting this week, on March 21st, March 22nd, or March 23rd @ 5:00 PM EDT = 2:00 PM PDT?

We know that Valerie and Matthew are available at that time, as are the two of us. If that time does not work, please suggest some alternative times.

Hope this is helpful,

Best,

Francis & Monib

[redacted]
barany@med.cornell.edu

[redacted]

Subject Privileged and Confidential: Cornell - Illumina Case Legal team only 2

From Francis Barany <barany@med.cornell.edu>

To: Roger Chin <Roger.Chin@lw.com>, Pearson, Matthew <mpearson@akingump.com>, Douglas Lumish (Doug.Lumish@lw.com) <Doug.Lumish@lw.com>, gregory.sobolski@lw.com <gregory.sobolski@lw.com>, Finst, Rip <Rip.Finst@thermofisher.com>, Boyle, Sean <sean.boyle@thermofisher.com>, Valerie Cross <vlc1@cornell.edu>, Brian Kelly <bjk44@cornell.edu>

Cc: Monib Zirvi <matzirvi@yahoo.com>, Francis Barany <barany@med.cornell.edu>

Date Mar 19, 2017 at 1:23 PM

Francis

[redacted]

barany@med.cornell.edu

[redacted]

Markman Cornell Illumina _03_17_2017…

Subject Privileged and Confidential: Cornell - Illumina Case Legal team only 3

From Francis Barany <barany@med.cornell.edu>

To: Roger Chin <Roger.Chin@lw.com>, Pearson, Matthew <mpearson@akingump.com>, Douglas Lumish (Doug.Lumish@lw.com) <Doug.Lumish@lw.com>, gregory.sobolski@lw.com <gregory.sobolski@lw.com>, Finst, Rip <Rip.Finst@thermofisher.com>, Boyle, Sean <sean.boyle@thermofisher.com>, Valerie Cross <vlc1@cornell.edu>, Brian Kelly <bjk44@cornell.edu>

Cc: Monib Zirvi <matzirvi@yahoo.com>, Francis Barany <barany@med.cornell.edu>

Date Mar 19, 2017 at 1:24 PM

Francis

[redacted]

barany@med.cornell.edu

[redacted]

Markman Cornell Illumina _03_17_2017…

Subject Privileged and Confidential: Cornell - Illumina Case Legal team only 5

From Francis Barany <barany@med.cornell.edu>

To: Roger Chin <Roger.Chin@lw.com>, Pearson, Matthew <mpearson@akingump.com>, Douglas Lumish (Doug.Lumish@lw.com) <Doug.Lumish@lw.com>, gregory.sobolski@lw.com <gregory.sobolski@lw.com>, Finst, Rip <Rip.Finst@thermofisher.com>, Boyle, Sean <sean.boyle@thermofisher.com>, Valerie Cross <vlc1@cornell.edu>, Brian Kelly <bjk44@cornell.edu>

Cc: Monib Zirvi <matzirvi@yahoo.com>, Francis Barany <barany@med.cornell.edu>

Date Mar 19, 2017 at 1:25 PM

Total of 5 emails sent to legal group, please confirm you got it.

Would you please let us know your availability for a webex meeting this week, on March 21st, March 22nd, or March 23rd @ 5:00 PM EDT = 2:00 PM PDT?

Thanks!

Francis

[redacted]

barany@med.cornell.edu

[redacted]

Markman Cornell Illumina _03_18_2017…

Subject Privileged and Confidential: Cornell - Illumina Case Legal team only 4

From Francis Barany <barany@med.cornell.edu>

To: Roger Chin <Roger.Chin@lw.com>, Pearson, Matthew <mpearson@akingump.com>, Douglas Lumish (Doug.Lumish@lw.com) <Doug.Lumish@lw.com>, gregory.sobolski@lw.com <gregory.sobolski@lw.com>, Finst, Rip <Rip.Finst@thermofisher.com>, Boyle, Sean <sean.boyle@thermofisher.com>, Valerie Cross <vlc1@cornell.edu>, Brian Kelly <bjk44@cornell.edu>

Cc: Monib Zirvi <matzirvi@yahoo.com>, Francis Barany <barany@med.cornell.edu>

Date Mar 19, 2017 at 1:25 PM

Francis

[redacted]

barany@med.cornell.edu

[redacted]

Markman Cornell Illumina _03_18_2017…

Subject RE: Privileged and Confidential: Cornell - Illumina Case Legal team only 1

From Doug.Lumish@lw.com <Doug.Lumish@lw.com>

To: <barany@med.cornell.edu>, <Roger.Chin@lw.com>, <mpearson@akingump.com>, <Gregory.Sobolski@lw.com>, <Rip.Finst@thermofisher.com>, <sean.boyle@thermofisher.com>, <vlc1@cornell.edu>, <bjk44@cornell.edu>

Cc: <matzirvi@yahoo.com>, <barany@med.cornell.edu>

Date Mar 19, 2017 at 1:28 PM

Thank you Francis. We will discuss with the legal team and circle back to you.

Regards,
Doug

From: Francis Barany <barany@med.cornell.edu<mailto:barany@med.cornell.edu>>
Date: Sunday, Mar 19, 2017, 10:20 AM
To: Chin, Roger (SF) <Roger.Chin@lw.com<mailto:Roger.Chin@lw.com>>, Pearson, Matthew <mpearson@akingump.com<mailto:mpearson@akingump.com>>, Lumish, Doug (SV) <Doug.Lumish@lw.com<mailto:Doug.Lumish@lw.com>>, Sobolski, Gregory (SF) <Gregory.Sobolski@lw.com<mailto:Gregory.Sobolski@lw.com>>, Rip.Finst@thermofisher.com <Rip.Finst@thermofisher.com<mailto:Rip.Finst@thermofisher.com>>, sean.boyle@thermofisher.com

<sean.boyle@thermofisher.com<mailto:sean.boyle@thermofisher.com>>, Valerie Cross <vlc1@cornell.edu<mailto:vlc1@cornell.edu>>

<vic1@cornell.edu<mailto:vic1@cornell.edu>>,
Brian Kelly
<bjk44@cornell.edu<mailto:bjk44@cornell.edu>>
Cc: Monib Zirvi
<matzirvi@yahoo.com<mailto:matzirvi@yahoo.com
>>, Francis Barany
<barany@med.cornell.edu<mailto:barany@med.cor
nell.edu>>
Subject: Privileged and Confidential: Cornell -
Illumina Case Legal team only 1

Dear Roger, Matthew, Doug, Greg, Rip, Sean, Valerie, and Brian,

After our last phone meeting, we were instructed by Cornell to rethink the claims in view of the Markman language, just as Roger presented in his excellent summary slide decks.

Over the past two weeks, we have uncovered additional facts, as well as provided an updated interpretation of the claims in view of the Markman language. Both a primary and an appendix deck will be emailed to you in this and follow-up emails.

We understand that due to the protective order in the case there are certain facts we may not be privy to, and thus our views may be incomplete. John Zebala's entire Syntrix case was based on the doctrine of equivalence, yet he prevailed twice. Likewise, we feel that our position is currently significantly stronger than John's was before he went to trial.

While I have had the pleasure of meeting both Rip and Matthew, I have not met Roger, Doug, Greg, or Sean in person. Hopefully, after this discussion, we will be able to schedule such an in-person meeting.

We are trained as scientists, and understand there are many legal issues that are not our field of expertise. However, we feel that we have been wronged, and we are confident that a jury will also agree with us.

It is not just that Illumina stole 16 out of our 4,633 zip codes. It is that Illumina stole them from an unpublished list at a time when they did not know

how to get encoding and decoding to work. It is that Illumina used those very same zip codes to demonstrate the decoding. It is that Illumina must have secretly replicated our own work on a spotted array, exactly as taught in '917, otherwise, they would not know if their bead arrays were correct. It is that those 16 zip codes were so critical in the early years of their work, that Illumina renamed them as their first 16 IllumaCodes. It is that those 16 were critical for their quality control checks. It is that in all universal zip code arrays, pooled hybridization checks are necessary for quality control, prior to use. It is that Mark Chee and Jian-Bing Fan admitted that "hybridization-based decoding procedure" was incontrovertibly linked to "a universal Zipcode array". It is that Illumina conveniently allowed two key witnesses, Mark Chee and Jian-Bing Fan to escape to China to avoid depositions in the summer/fall or 2015.

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Thus, in reviewing the slides enclosed in the follow-up emails, in addition to wearing your legal hat, think if this happened to your brother, and what you would do to protect his rights.

In discussion with Valerie, she recommended a follow-up webex. Would you kindly let us know your

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Hope this is helpful,

Best,

Francis & Monib

[redacted]
[redacted]
barany@med.cornell.edu<mailto:barany@med.cornell.edu>

[redacted]

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Latham & Watkins LLP

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Subject Re: Privileged and Confidential: Cornell - Illumina Case Legal team only 1

From Monib Zirvi <matzirvi@yahoo.com>

To: <Doug.Lumish@lw.com>

Cc: <barany@med.cornell.edu>, <Roger.Chin@lw.com>, <mpearson@akingump.com>, <Gregory.Sobolski@lw.com>, <Rip.Finst@thermofisher.com>, <sean.boyle@thermofisher.com>, <vlc1@cornell.edu>, <bjk44@cornell.edu>

Date Mar 19, 2017 at 1:33 PM

It is that JB Fan attended this meeting on September 11th, 2016 in China with the head of Market Development for Illumina in China, Jerry Wang at a time that Illumina claimed that they did not know where he was.

Sent from my iPhone

> On Mar 19, 2017, at 1:28 PM, <Doug.Lumish@lw.com> <Doug.Lumish@lw.com> wrote:
>
> Thank you Francis. We will discuss with the legal team and circle back to you.
>
> Regards,
> Doug
>
>
>
>

> From: Francis Barany <barany@med.cornell.edu<mailto:barany@med.cornell.edu>>

nell.edu>>
> Date: Sunday, Mar 19, 2017, 10:20 AM
> To: Chin, Roger (SF)
<Roger.Chin@lw.com<mailto:Roger.Chin@lw.com>
>, Pearson, Matthew
<mpearson@akingump.com<mailto:mpearson@aki
ngump.com>>, Lumish, Doug (SV)
<Doug.Lumish@lw.com<mailto:Doug.Lumish@lw.co
m>>, Sobolski, Gregory (SF)
<Gregory.Sobolski@lw.com<mailto:Gregory.Sobolsk
i@lw.com>>, Rip.Finst@thermofisher.com
<Rip.Finst@thermofisher.com<mailto:Rip.Finst@the
rmofisher.com>>, sean.boyle@thermofisher.com
<sean.boyle@thermofisher.com<mailto:sean.boyle
@thermofisher.com>>, Valerie Cross
<vlc1@cornell.edu<mailto:vlc1@cornell.edu>>,
Brian Kelly
<bjk44@cornell.edu<mailto:bjk44@cornell.edu>>
> Cc: Monib Zirvi
<matzirvi@yahoo.com<mailto:matzirvi@yahoo.com
>>, Francis Barany
<barany@med.cornell.edu<mailto:barany@med.cor
nell.edu>>
> Subject: Privileged and Confidential: Cornell -
Illumina Case Legal team only 1
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> Hope this is helpful,
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> Best,
>
> Francis & Monib
>
>[redacted]
>[redacted]
>
barany@med.cornell.edu<mailto:barany@med.cornell.edu>
>
>[redacted]
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Subject Re: Privileged and Confidential: Source Code

From Pearson, Matthew <mpearson@AKINGUMP.com>

To: Francis Barany <barany@med.cornell.edu>

Cc: Valerie Cross <vlc1@cornell.edu>, Monib Zirvi <matzirvi@yahoo.com>

Date Mar 19, 2017 at 2:26 PM

Francis -

To be clear, I think you are over interpreting our discussion. As always, I will not reveal information produced as confidential in the litigation.

Thanks,
Matt

Sent from my iPhone

On Mar 19, 2017, at 1:11 PM, Francis Barany <barany@med.cornell.edu> wrote:

> Dear Matthew and Valerie,
>
> Thank you for speaking with us on Friday. We will send out the revised deck with the new analysis of the claims using the "Markman wording" in a follow-up email.
>
> Matthew, in our discussion, it appears that Illumina DID NOT REVEAL the SOURCE CODE to you FOR THEIR COMPUTER PROGRAMS used to generate their early zip code sequences, NOR THEIR DMAP DLL FILES SOURCE CODES. Also, when we asked about whether they released certain sequences, you said you had to "look at your notes".
>
> We are thus re-sending you our comments/questions from February 20th below (updated a bit), which we believe are more relevant than ever, since we now know the dll files are required for at least some of Illumina's sequencing

required for at least some of Illumina's sequencing instruments as well. It is our view that Illumina had a systematic and willful program to try and hide their use of zipcode arrays, including using about a dozen other names, and that intensified after Illumina filed an Antitrust suit against ABI in 2004 (which we only learned about in the last two weeks).

We are not requesting you to reveal the sequences that are mentioned in the various applications. Matthew, would you please look at your notes and go back over the documents/files submitted, to understand if Illumina provided to YOU the full sequences for:

1. A set of 16 adapters Kevin Gunderson claims are "in use" in the Illumina provisional application 60/135,123 filed on May 20, 1999? Gunderson also claims an additional 100 will be prepared, do you have those?

2. A set of 128 unique "universal Zipcode array" addresses in the Illumina provisional application 60/180810, filed Feb. 7, 2000 with only Jian-Bing Fan as inventor?

Looking forward to speaking next week.

Best,

Francis & Monib

[redacted]
barany@med.cornell.edu

[redacted]

As you know, Illumina does not make addressable arrays. They make assembled arrays. The beads go into random places, and if you use an assembled array "as is" to try to identify SNPs or look at expression data, you will see a bunch of random red or green fluorescent spots, and it is impossible to interpret.

To interpret the data, one needs addressable arrays. There are two

To interpret the data, one needs addressable arrays. There are two ways to make addressable arrays – you can put your zipcode oligos down at known locations in an X-Y coordinate, or you can use zipcodes to decode where randomly distributed oligos (i.e. on beads) have been placed, again in an X-dimension and in a Y-dimension. When using the second approach, one then needs a "cheat sheet" for each array you make, that tells you which bead is in which well, by giving the X coordinate and the Y coordinate (called the BeadMap). That is the DMAP file you refer to in your email.

This was the key moment in the Zebala case, when David Walt admitted that to decode the arrays you just needed to know two dimensions, the X-dimension and the Y-dimension (see enclosed revised deck). You will also notice part 5, the red box at the bottom that says "Name: string zipcode", and then beneath that "Xvalues" and "Yvalues".

It is mission critical for us to see the original programing code, also known as the "source code" for the original dll files, for example in SQL, or C++, or Microsoft.net, or Java, or JavaScript, or other programing languages. That is different from the files Monib downloaded, or the DMAP files that are made for each separate Beadchip. By way of example, in our own patent listing about 4,000 zipcodes (initially published as WO2001079548), we wrote a program to make sure there wouldn't be cross-hybridization problems between a zipcode the sequence at the junction of another zipcode and target sequence (i.e. the composite oligo) – this was several hundred lines of code and took up 13 pages in a printout (enclosed, Fig. 35). As you can see, the original program often has comments that explain what is being done in the program.

Likewise, we strongly suspect – given that the compiled listing already links the words "zipcode" with "Xvalues" and "Yvalues" that the source code would clearly delineates exactly what is going on in the program.

The key reason this is important is because Illumina claims their arrays — including the infinium SNP & copynumber BeadChip, infinium methylation BeadChip, and expression BeadChip arrays — are not "zipcode" arrays.

We all know this is not true. WE believe a compelling argument can be made that Illumina's failure to release the original source code for the "Common Verascan.dll", and "Illumina datafiles.dll" files (and additional programs as detailed below) was to HIDE their own admission that all their arrays are really zipcode arrays, and this constitutes willful concealment of material facts.

Now it is time for Judge Stark to know in no uncertain terms that Illumina has mislead him, that the Illumina Infinium BeadChips and all other Illumina array products are all zipcode arrays.

are all zipcode arrays.

Furthermore…

We only recently uncovered that in Illumina's initial submition of provisional application 60/227,948 (M. Chee and K. Gunderson) on August 25, 2000, they called our zip codes as "IllumaCodes". In Illumina's full application 09/940,185 filed on August 27, 2001 (K. Gunderson & M. Chee), they renamed them as "Seq. ID No.", and further, only provided the sequence information as scanned tables. The USPTO wrote a letter to Illumina on October 19, 2001 stating that applicants must provide an initial computer readable form (CRF) copy. Illumina obviously tried to limit the USPTO's ability to search the sequences, despite the fact they were clearly generated on a computer.

Since the GoldenGate assay, and other Illumina publication refer to our zip codes as "IllumiCode" (trademarked) array, and the individual addresses as "illumiCodes" (i.e. illumiCode # 561, #217, #1024), it would not be unreasonable to hypothesize that there is some overlap between the list of "IllumaCodes" and "illumiCodes". (Put another way, the probability of randomly choosing two names where 9 of 10 letters match in order is 26 to the 9th power, which is 1 in 5.4 trillion, or to put it in DNA language, there would be substantial cross-hybridization!).

Adding to this, in the First Amendment to the Joint Development Agreement, signed by John R. Stuelpnagel and dated March 27, 2001 (in other words before the August 27, 2001 submission), there is a call for defining and developing "Tag Sequences for the Collaboration Product", which we all now know are just another name for zipcode sequences.

All such sequences are covered by the '917 family of patents. This leads us to the following questions:

1. Did Illumina provide the SOURCE CODES for the "Common Verascan.dll", and "Illumina datafiles.dll" files – both of which contain the word "zipcode" -- to Akin Gump?

2. Did Illumina provide the SOURCE CODES for the software they wrote to generate the initial "IllumaCodes", and all subsequent revisions to Akin Gump? Do these programs contain the word "zipcode"?

3. Did the SOURCE CODES for the software they wrote to generate the initial "IllumaCodes" contain the initial 16 zipcodes

from Barany's original unpublished 465 list, or did they add them afterwards to the tables in their US20030096239 patent application?

4. Did the SOURCE CODES for the software they wrote to generate the initial "IllumaCodes" contain a subroutine to check a new probe sequences against all previous decoder sequences for complementarity scores of < 14 (less than 14) of which there are 1,461 pairs that do not follow that rule in the 4,000 "IllumaCodes" listed in table 1, or did the source code use the term "<= 18" (less than or equal to, which is exactly what Barany taught)?

5. Did Illumina provide the SOURCE CODES for the "Tag

Sequences for the Collaboration Product", and all subsequent revisions to Akin Gump? Do these programs contain the word "zipcode"?

6. Did Illumina provide the SOURCE CODES for the software they wrote to generate the current set of "IllumiCodes" or whatever they are calling the zipcodes on their current "Illumina infinium humanmethylation450 beadchip" "llumina Infinium HD BeadChip", "Sentrix Universal Array Matrix", "Illumina Human Whole-Genome DASL HT Assay", "HumanHT-12 v4 Expression BeadChip", or any other arrays sold by Illumina, and all subsequent revisions to Akin Gump? Do these programs contain the word "zipcode"?

7. Do you know which of Illumina's current and prior BeadChip products use our original 16 zip codes? The 60/172,106 Kevin Gunderson application as originally filed on Dec. 23, 1999? The 60/180810 provisional application, Filed Feb. 7, 2000 with Jian-Big Fan as the only inventor, that refers to universal BeadArrays with 128 unique addresses (zipcodes)?

If Illumina did not reveal the SOURCE CODE, i.e. original programing code, can we force them in court with a motion, such that we reveal their willful concealment of material facts?

Would this be grounds for appeal, if the SOURCE CODE was never revealed to Judge Stark and the Cornell legal team?

If Illumina did reveal the SOURCE CODE information, can we inform Judge Stark that Illumina themselves refer to the addresses on said infinium arrays as "zipcodes" contradicting their prior assertion that these are not zipcode arrays?

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us immediately by e-mail, and delete the original message.

Subject Re: Privileged and Confidential: Source Code

From Monib Zirvi <matzirvi@yahoo.com>

To: Pearson, Matthew <mpearson@AKINGUMP.com>

Cc: Francis Barany <barany@med.cornell.edu>, Valerie Cross <vlc1@cornell.edu>

Date Mar 19, 2017 at 2:54 PM

Dear Matthew,

The fact that Illumina has been shown to have lied in the prosecution history and submissions of multiple patents and clearly has lied about knowing the whereabouts of key witnesses means that it is very reasonable to be concerned that they may have knowingly withheld materially relevant facts in the discovery phase. I believe that knowingly withholding a fact such as the fact that the word Zipcode is used is the SOURCE CODE for the DLL files used in their DMAP software is very relevant. If they had turned over the SOURCE CODE, that is fine, but if they haven't, that is materially relevant and may open them up for default judgment or some other penalty. This is the reason the inventors are all so concerned about this issue and other similar issues.

Sincerely,

Monib

Sent from my iPhone

On Mar 19, 2017, at 2:26 PM, Pearson, Matthew <mpearson@AKINGUMP.com> wrote:

Francis -

To be clear, I think you are over interpreting our discussion. As always, I will not reveal information produced as confidential in the litigation.

Thanks

Thanks,
Matt

Sent from my iPhone

On Mar 19, 2017, at 1:11 PM, Francis Barany <barany@med.cornell.edu> wrote:

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an additional 100 will be prepared, do you have those?

2. A set of 128 unique "universal Zipcode array" addresses in the Illumina provisional application 60/180810, filed Feb. 7, 2000 with only Jian-Bing Fan as inventor?

Looking forward to speaking next week.

Best,

Francis & Monib

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

As you know, Illumina does not make addressable arrays. They make assembled arrays. The beads go into random places, and if you use an assembled array "as is" to try to identify SNPs or look at expression data, you will see a bunch of random red or green fluorescent spots, and it is impossible to interpret.

To interpret the data, one needs addressable arrays. There are two ways to make addressable arrays – you can put your zipcode oligos down at known locations in an X-Y coordinate, or you can use zipcodes to decode where randomly distributed oligos (i.e. on beads) have been placed, again in an X-dimension and in a Y-dimension. When using the second approach, one then needs a "cheat sheet" for each array you make, that tells you which bead is in which well, by giving the X coordinate and the Y coordinate (called the BeadMap). That is the DMAP file you refer to in your email.

This was the key moment in the Zebala case, when David Walt admitted that to decode the arrays you just needed to know two dimensions, the X-dimension and the Y-dimension (see enclosed revised deck). You will also notice part 5, the red box at the bottom that says "Name: string zipcode", and then beneath that "Xvalues"

and "Yvalues".

It is mission critical for us to see the original programing code, also known as the "source code" for the original dll files, for example in SQL, or C++, or Microsoft.net, or Java, or JavaScript, or other programing languages. That is different from the files Monib downloaded, or the DMAP files that are made for each separate Beadchip. By way of

example, in our own patent listing about 4,000 zipcodes (initially published as WO2001079548), we wrote a program to make sure there wouldn't be cross-hybridization problems between a zipcode the sequence at the junction of another zipcode and target sequence (i.e. the composite oligo) – this was several hundred lines of code and took up 13 pages in a printout (enclosed, Fig. 35). As you can see, the original program often has comments that explain what is being done in the program.

Likewise, we strongly suspect – given that the compiled listing already links the words "zipcode" with "Xvalues" and "Yvalues" that the source code would clearly delineates exactly what is going on in the program.

The key reason this is important is because Illumina claims their arrays — including the infinium SNP & copynumber BeadChip, infinium methylation BeadChip, and expression BeadChip arrays — are not "zipcode" arrays.

We all know this is not true. WE believe a compelling argument can be made that Illumina's failure to release the original source code for the "Common Verascan.dll", and "Illumina datafiles.dll" files (and additional programs as detailed below) was to HIDE their own admission that all their arrays are really zipcode arrays, and this constitutes willful concealment of material facts.

Now it is time for Judge Stark to know in no uncertain terms that Illumina has mislead him, that the Illumina Infinium BeadChips and all other Illumina array products are all zipcode arrays.

Furthermore…

We only recently uncovered that in Illumina's initial submition of provisional application 60/227,948 (M. Chee and K. Gunderson) on August 25, 2000, they called our zip codes as "IllumaCodes". In Illumina's full application 09/940,185 filed on August 27, 2001 (K. Gunderson & M. Chee), they renamed them as "Seq. ID No.", and further, only provided the sequence information as scanned tables. The USPTO wrote a letter to Illumina on October 19, 2001 stating that applicants must provide an initial computer readable form (CRF) copy. Illumina obviously tried to limit the USPTO's ability to search the sequences, despite the fact they were clearly generated on a computer.

Since the GoldenGate assay, and other Illumina publication refer to our zip codes as "IllumiCode" (trademarked) array, and the individual addresses as "illumiCodes" (i.e. illumiCode # 561, #217, #1024), it would not be unreasonable to hypothesize that there is some overlap between the list of "IllumaCodes" and "illumiCodes". (Put another way, the probability of randomly choosing two names where 9 of 10 letters match in order is 26 to the 9th power, which is 1 in 5.4 trillion, or to put it in DNA language, there would be substantial cross-hybridization!).

Adding to this, in the First Amendment to the Joint Development Agreement, signed by John R. Stuelpnagel and dated March 27, 2001 (in other words before the August 27, 2001 submission), there is a call for defining and developing "Tag Sequences for the Collaboration Product", which we all now know are just another name for zipcode sequences.

All such sequences are covered by the '917 family of patents. This leads us to the following questions:

1. Did Illumina provide the SOURCE CODES for the "Common Verascan.dll", and "Illumina datafiles.dll" files – both of which contain the word "zipcode" -- to Akin Gump?

2. Did Illumina provide the SOURCE CODES for the software they wrote to generate the initial "IllumaCodes", and all subsequent revisions to Akin Gump? Do these programs contain the word "zipcode"?

3. Did the SOURCE CODES for the software they wrote to generate the initial "IllumaCodes" contain the initial 16 zipcodes from Barany's original unpublished 465 list, or did they add them afterwards to the tables in their US20030096239 patent application?

4. Did the SOURCE CODES for the software they wrote to generate the initial "IllumaCodes" contain a subroutine to check a new probe sequences against all previous decoder sequences for complementarity scores of < 14 (less than 14) of which there are 1,461 pairs that do not follow that rule in the 4,000 "IllumaCodes" listed in table 1, or did the source code use the term "<= 18" (less than or equal to, which is exactly what Barany taught)?

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Subject Re: Privileged and Confidential: Source Code

From Francis Barany <barany@med.cornell.edu>

To: Pearson, Matthew <mpearson@AKINGUMP.com>

Cc: Valerie Cross <vlc1@cornell.edu>, Monib Zirvi <matzirvi@yahoo.com>

Date Mar 19, 2017 at 3:15 PM

Dear Matthew,

Monib said it more eloquently than I did, so thank you for understanding that we are not trying to trick you into breaking the protective order. We are just trying to ascertain whether Illumina came clean on all the items they are supposed to. We are just asking for a simple "yes" or "no" answer to our questions. Maybe I don't fully understand the protective order, so pardon my ignorance. If we find out about something through deep internet searches, and it turns out Illumina did not realize we would uncover it, and they "forgot" to hand over that material in discovery, then that would appear to be an important finding. Am I missing something here?

Good luck at the Tyagi deposition tomorrow.

Best,

Francis
Sent from my iPhone

On Mar 19, 2017, at 2:54 PM, Monib Zirvi <matzirvi@yahoo.com> wrote:

> Dear Matthew,
>
> The fact that Illumina has been shown to have lied in the prosecution history and submissions of multiple patents and clearly has lied about knowing the whereabouts of key witnesses means that it is very reasonable to be concerned that they may have knowingly withheld materially relevant facts in

have knowingly withheld materially relevant facts in the discovery phase. I believe that knowingly withholding a fact such as the fact that the word Zipcode is used is the SOURCE CODE for the DLL files used in their DMAP software is very relevant. If they had turned over the SOURCE CODE, that is fine, but if they haven't, that is materially relevant and may open them up for default judgment or some other penalty. This is the reason the inventors are all so concerned about this issue and other similar issues.

Sincerely,

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Subject Jian-Bing Fan

From Monib Zirvi <matzirvi@yahoo.com>

To: Valerie Cross Dorn <vlc1@cornell.edu>, <sean.boyle@thermofisher.com>, <roger.chin@lw.com>, <Rip.Finst@thermofisher.com>, <mpearson@akingump.com>, <barany@med.cornell.edu>, <Doug.Lumish@lw.com>, <bjk44@cornell.edu>

Date Mar 19, 2017 at 8:47 PM

Jian-Bing Fan also was a keynote speaker on June 22, 2016 in San Francisco at the Liquid Biopsy Summit.

http://liquidbiopsysummit.com/uploadedFiles/Liquid_Biopsy_Summit/Agenda/16/2016-The-Liquid-Biopsy-Summit-Brochure.pdf

Sent from my iPhone

2016-The-Liquid-Biopsy-Summit-Broch…

Subject Re: Privileged and Confidential: Cornell - Illumina Case Legal team only 1

From Valerie Cross Dorn <vlc1@cornell.edu>

To: Francis Barany <barany@med.cornell.edu>

Cc: Roger.Chin@lw.com <Roger.Chin@lw.com>, Matt Pearson <mpearson@akingump.com>, Doug.Lumish@lw.com <Doug.Lumish@lw.com>, gregory.sobolski@lw.com <gregory.sobolski@lw.com>, Rip.Finst@thermofisher.com <Rip.Finst@thermofisher.com>, sean.boyle@thermofisher.com <sean.boyle@thermofisher.com>, Brian Kelly <bjk44@cornell.edu>, Monib Zirvi <matzirvi@yahoo.com>

Date Mar 20, 2017 at 10:01 PM

Francis, I have not had any opportunity to connect with Latham Watkins or Life regarding your email regarding a web ex this week, but I do want to address the opening statement in your email below. It is not clear to me what you are referring to in the "instructed by Cornell" statement. I did not issue any instruction to you, and I am not aware that anyone else at Cornell gave an instruction for you to perform the analysis that you are now presenting.

You are correct that you do not have all of the facts relevant to the issues we have been discussing. I will look forward to a further discussion with Matt, Roger, and Rip, who do have access to the relevant facts, and hope that we can work together to achieve a better understanding of the limitations and risks we face that are motivating the current settlement discussion.

Valerie Cross Dorn
Associate University Counsel

Associate University Counsel
Cornell University
[redacted]

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Over the past two weeks, we have uncovered additional facts, as well as provided an updated interpretation of the claims in view of the Markman language. Both a primary and an appendix deck will be emailed to you in this and follow-up emails.

We understand that due to the protective order in the case there are certain facts we may not be privy to, and thus our views may be incomplete. John Zebala's entire Syntrix case was based on the doctrine of equivalence, yet he prevailed twice. Likewise, we feel that our position is currently significantly stronger than John's was before he went to trial.

While I have had the pleasure of meeting both Rip and Matthew, I have not met Roger, Doug, Greg, or Sean in person. Hopefully, after this discussion, we will be able to schedule such an in-person meeting.

We are trained as scientists, and understand there are many legal issues that are not our field of expertise. However, we feel that we have been wronged, and we are confident that a jury will also agree with us.

It is not just that Illumina stole 16 out of our 4,633 zip codes. It is that Illumina stole them from an unpublished list at a time when they did not

know how to get encoding and decoding to work. It is that Illumina used those very same zip codes to demonstrate the decoding. It is that Illumina must have secretly replicated our own work on a spotted array, exactly as taught in '917, otherwise, they would not know if their bead arrays were correct. It is that those 16 zip codes were so critical in the early years of their work, that Illumina renamed them as their first 16 IllumaCodes. It is that those 16 were critical for their quality control checks. It is that in all universal zip code arrays, pooled hybridization checks are necessary for quality control, prior to use. It is that Mark Chee and Jian-Bing Fan admitted that "hybridization-based decoding procedure" was incontrovertibly linked to "a universal Zipcode array". It is that Illumina conveniently allowed two key witnesses, Mark Chee and Jian-Bing Fan to escape to China to avoid depositions in the summer/fall or 2015.

It is that Illumina tried and failed to commercialize 7 other techniques to decode their arrays, and the final address encoders they used were zip codes. It is that Illumina used our teachings to create all subsequent zip codes, as derivatives of our original 16 zip codes. It is that Illumina willfully tried to deceive the USPTO, by sending only scanned tables, so the USPTO could not do sequence searches, and renaming them as "Seq. ID. No." instead of "IllumaCodes". It is that Illumina willfully tried to deceive investors and customers that they invented addressable arrays (when in fact they only invented assembled arrays), in part by using a dozen different names for zip codes. It is that Illumina willfully tried to deceive Judge Stark into believing that Infinium BeadChips are "hybridization arrays", while to this day, Illumina still secretly uses the word "zipcode" in the dll files that are required for every DMAP file decoding of an Infinium or Universal Sentrix BeadChip.

Thus, in reviewing the slides enclosed in the follow-up emails, in addition to wearing your legal hat, think if this happened to your brother, and what you would do to protect his rights.

In discussion with Valerie, she recommended a follow-up webex. Would you kindly let us know your availability for a webex meeting this week, on March 21st, March 22nd, or March 23rd @ 5:00 PM EDT = 2:00 PM PDT?

We know that Valerie and Matthew are available at that time, as are the two of us. If that time does not work, please suggest some alternative times.

Hope this is helpful,

Best,

Francis & Monib

[redacted]
barany@med.cornell.edu

[redacted]

View less

Subject Re: Privileged and Confidential: Cornell - Illumina Case Legal team only 1

From Monib Zirvi <matzirvi@yahoo.com>

To: Valerie Cross Dorn <vlc1@cornell.edu>

Cc: Francis Barany <barany@med.cornell.edu>, Roger.Chin@lw.com <Roger.Chin@lw.com>, Matt Pearson <mpearson@akingump.com>, Doug.Lumish@lw.com <Doug.Lumish@lw.com>, gregory.sobolski@lw.com <gregory.sobolski@lw.com>, Rip.Finst@thermofisher.com <Rip.Finst@thermofisher.com>, sean.boyle@thermofisher.com <sean.boyle@thermofisher.com>, Brian Kelly <bjk44@cornell.edu>

Date Mar 20, 2017 at 10:14 PM

There are publications by Illumina as late as 2008 which clearly show Zipcode capture using a Universal Zipcode array. Considering Illumina started in 1998, that is a decade of literal infringement of Cornell IP. In addition, if they are truly using short (16 bases or less) decoders now, they have indicated in some recent public patents that they use sequencing by extension to extend these and thus create 17 base oligonucleotides or greater. In that case the first 17 bases are Zipcode sequence any additional bases added qualify as target sequence because they are added enzymatically and are homologous to naturally occurring DNA.

Here is also straightforward analogy that may help explain doctrine of equivalence

If hybridization arrays were considered just plain toast,

Then Universal Zip Code arrays are like a peanut butter and jelly sandwich. Using LDR vs Gap LDR is similar to mentioning that you could use either crunchy or smooth peanut butter in the sandwich and have it still be a peanut butter and jelly sandwich.

Illumina for Sentrix/golden gate and other products just tries to flip which side has peanut butter and jelly and calls it something different (see probes and decoders oligonucleotide application where they used Zipcodes as probes)

For Infinium products it just adds a extra piece of toast to the sandwich. It's still a peanut butter and jelly sandwich, no matter how you slice it. Trying to use short decoders is like putting less peanut butter than jelly...it's still a peanut butter and jelly sandwich.

Finding Zipcode in patents and software is equivalent to finding the abbreviation PB&J everywhere.

Sent from my iPhone

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barany@med.cornell.edu

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View less

Subject Re: Privileged and Confidential: Cornell - Illumina Case Legal team only 1

From Francis Barany <barany@med.cornell.edu>

To: Valerie Cross <vlc1@cornell.edu>, Brian J. Kelly <bjk2003@med.cornell.edu>

Cc: Roger.Chin@lw.com <Roger.Chin@lw.com>, Matt Pearson <mpearson@akingump.com>, Doug.Lumish@lw.com <Doug.Lumish@lw.com>, gregory.sobolski@lw.com <gregory.sobolski@lw.com>, Rip.Finst@thermofisher.com <Rip.Finst@thermofisher.com>, sean.boyle@thermofisher.com <sean.boyle@thermofisher.com>, Brian Kelly <bjk44@cornell.edu>, Monib Zirvi <matzirvi@yahoo.com>

Date Mar 21, 2017 at 6:44 AM

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It is not just that Illumina stole 16 out of our 4,633 zip codes. It is that Illumina stole them from an unpublished list at a time when they did not know how to get encoding and decoding to work. It is that Illumina used those very same zip codes to demonstrate the decoding. It is that Illumina must have secretly replicated our own work on a spotted array, exactly as taught in '917, otherwise, they would not know if their bead arrays were correct. It is that those 16 zip codes were so critical in the early years of their work, that Illumina renamed them as their first 16 IllumaCodes. It is that those 16 were critical for their quality control checks. It is that in all universal zip code arrays, pooled hybridization checks are necessary for quality control, prior to use. It is that Mark Chee and Jian-Bing Fan admitted that "hybridization-based decoding procedure" was incontrovertibly linked to "a universal Zipcode array". It is that Illumina conveniently allowed two key witnesses, Mark Chee and Jian-Bing Fan to escape to China to avoid depositions in the summer/fall or 2015.

It is that Illumina tried and failed to commercialize 7 other techniques to decode their arrays, and the final address encoders they used were zip codes. It is that Illumina used our teachings to create all subsequent zip codes, as derivatives of our original 16 zip codes. It is that Illumina willfully tried to deceive the USPTO, by sending only scanned tables, so the USPTO could not do sequence searches, and renaming them as "Seq. ID. No." instead of "IllumaCodes". It is that Illumina willfully tried to deceive investors and customers that they invented addressable arrays (when in fact they only invented assembled arrays), in part by using a dozen different names for zip codes. It is that Illumina willfully tried to deceive Judge Stark into believing that Infinium BeadChips are "hybridization arrays", while to this day, Illumina still secretly uses the word "zipcode" in the dll files that are required for every DMAP file decoding of an Infinium or Universal Sentrix BeadChip.

Thus, in reviewing the slides enclosed in the follow-up emails, in addition to wearing your legal hat, think if this happened to your brother, and what you would do to protect his rights.

In discussion with Valerie, she recommended a follow-up webex. Would you kindly let us know your availability for a webex meeting this week, on March 21st, March 22nd, or March 23rd @ 5:00 PM EDT = 2:00 PM PDT?

We know that Valerie and Matthew are available at that time, as are the two of us. If that time does not work, please suggest some alternative times.

Hope this is helpful,

Best,

Francis & Monib

[redacted]

[redacted]
barany@med.cornell.edu
[redacted]

View less

Subject Little bit of injustice

From Monib Zirvi <matzirvi@yahoo.com>

To: <barany@med.cornell.edu>

Cc: Valerie Cross Dorn <vlc1@cornell.edu>, <sean.boyle@thermofisher.com>, <roger.chin@lw.com>, <Rip.Finst@thermofisher.com>, <mpearson@akingump.com>, <barany@med.cornell.edu>, <Doug.Lumish@lw.com>, <bjk44@cornell.edu>

Date Mar 24, 2017 at 11:09 AM

The inventors do not want to be the victims of "a little bit of injustice". The final 10% of findings may make a huge difference in this case. We would be greatly relieved and really appreciate it if the excellent attorneys on this case can find a way to let Judge Stark know.

Chief Judge Rader Sets the Stage

The CLE presentation began with Federal Circuit Court of Appeals Chief Judge Randall Rader singing Bob Dylan's "The Times They Are A-Changin'" with new lyrics emphasizing needed changes in U.S. patent litigation. After his musical interlude, Judge Rader went on to talk about the unreasonably high cost of patent litigation in the U.S. as opposed to other countries — which is largely the result of the broad discovery allowed in the U.S. — and the difficulties in attempting to categorize and curb "patent trolls" through legislation.

He believes that district court judges are in the best position to recognize and stop abusive litigation practices. As to out-of-control litigation costs, Judge Rader proposed limiting the amount of discovery because 90 percent of the relevant documents are known to the parties before discovery even begins. He said he "believes in a little injustice," meaning that ignoring the final 10 percent of the documents would have only a de minimus effect on outcomes in exchange for a dramatic increase in efficiency.

The District of Delaware's Patent Study Group

https://www.law360.com/articles/539183/another-delaware-judge-outlines-new-patent-case-practices

Sent from my iPhone

Subject IPR2016-00557, No. 2035-8 Exhibit - Declaration of Monib Zirvi (P.T.A.B. Nov. 8, 2016)

From Monib Zirvi <matzirvi@yahoo.com>

To: <barany@med.cornell.edu>

Cc: Valerie Cross Dorn <vlc1@cornell.edu>, <sean.boyle@thermofisher.com>, <roger.chin@lw.com>, <Rip.Finst@thermofisher.com>, <mpearson@akingump.com>, <barany@med.cornell.edu>, <Doug.Lumish@lw.com>, <bjk44@cornell.edu>, <cnathan@med.cornell.edu>

Date Mar 26, 2017 at 1:57 PM

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Sincerely,

Dr. Monib Zirvi, MD/PhD
Cornell University Medical College, Class of 2000

Sent from my iPhone

Subject RE: IPR2016-00557, No. 2035-8
Exhibit - Declaration of Monib Zirvi
(P.T.A.B. Nov. 8, 2016)

From Doug.Lumish@lw.com
<Doug.Lumish@lw.com>

To: <matzirvi@yahoo.com>,
<barany@med.cornell.edu>

Cc: <vlc1@cornell.edu>,
<sean.boyle@thermofisher.com>,
<Roger.Chin@lw.com>,
<Rip.Finst@thermofisher.com>,
<mpearson@akingump.com>,
<barany@med.cornell.edu>,
<bjk44@cornell.edu>,
<cnathan@med.cornell.edu>

Date Mar 27, 2017 at 5:27 PM

Francis and Monib,

We received your recent emails, and we understand the concerns you have articulated about Illumina's business strategy and litigation tactics. Those concerns have been taken into account by Cornell and Thermo Fisher as they consider their options. We will be in a better position to consider further steps after the parties decide how they want to handle the specific patent claims in relation to their ongoing discussions. In the meantime, we get your point and appreciate your passion, and we will let you know if we need more information from you. Roger will separately respond in more detail to some of the substantive points you have raised.

Thanks,
Doug

Douglas E. Lumish

LATHAM & WATKINS LLP
[redacted]

-----Original Message-----
From: Monib Zirvi [mailto:matzirvi@yahoo.com]

From: Monib Zirvi [mailto:matzirvi@yahoo.com]
Sent: Sunday, March 26, 2017 10:57 AM
To: barany@med.cornell.edu
Cc: Valerie Cross Dorn <vlc1@cornell.edu>;
sean.boyle@thermofisher.com; Chin, Roger (SF)
<Roger.Chin@lw.com>;
Rip.Finst@thermofisher.com;
mpearson@akingump.com;
barany@med.cornell.edu; Lumish, Doug (SV)
<Doug.Lumish@lw.com>; bjk44@cornell.edu;
cnathan@med.cornell.edu
Subject: IPR2016-00557, No. 2035-8 Exhibit -
Declaration of Monib Zirvi (P.T.A.B. Nov. 8, 2016)

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Cornell University Medical College, Class of 2000

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Latham & Watkins LLP

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Subject Privileged Re: Cornell vs. Illumina, strategy.

From Francis Barany <barany@med.cornell.edu>

To: Doug.Lumish@lw.com <Doug.Lumish@lw.com>, Roger Chin <Roger.Chin@lw.com>

Cc: Monib Zirvi <matzirvi@yahoo.com>, Valerie Cross <vlc1@cornell.edu>, Boyle, Sean <sean.boyle@thermofisher.com>, Finst, Rip <Rip.Finst@thermofisher.com>, mpearson@akingump.com <mpearson@akingump.com>, Brian Kelly <bjk44@cornell.edu>, Carl F. Nathan <cnathan@med.cornell.edu>, Francis Barany <barany@med.cornell.edu>

Date Mar 27, 2017 at 6:07 PM

Dear Doug and Roger,

Thank you for your positive feedback.

We recognize you do not have an easy task in front of you, and are trying to provide you with the underlying information so as to help you prepare for the trial, or improve your negotiating position. Although we understand that due to the protective order we may not have all the facts, nevertheless, we believe there are sufficient clues for demonstrating willful infringement.

Roger, we know how persuasive you can be, both verbally and in your slide presentations. We do not want to create extra work for you, but do request a dialogue to explore different arguments and counterarguments together, such that we are all working as one team. In our view, an in person meeting would be the most effective way to achieving this goal in a timely manner.

Looking forward to your thoughts on how to proceed,

Best,

Francis & Monib

[redacted]
barany@med.cornell.edu

[redacted]

> On Mar 27, 2017, at 5:27 PM,
> Doug.Lumish@lw.com wrote:
>
> Francis and Monib,
>
> We received your recent emails, and we understand the concerns you have articulated about Illumina's business strategy and litigation tactics. Those concerns have been taken into account by Cornell and Thermo Fisher as they consider their options. We will be in a better position to consider further steps after the parties decide how they want to handle the specific patent claims in relation to their ongoing discussions. In the meantime, we get your point and appreciate your passion, and we will let you know if we need more information from you. Roger will separately respond in more detail to some of the substantive points you have raised.
>
> Thanks,
> Doug
>
> Douglas E. Lumish
>
> LATHAM & WATKINS LLP
> [redacted]
>
> -----Original Message-----
> From: Monib Zirvi [mailto:matzirvi@yahoo.com]
> Sent: Sunday, March 26, 2017 10:57 AM

To: barany@med.cornell.edu
Cc: Valerie Cross Dorn <vlc1@cornell.edu>; sean.boyle@thermofisher.com; Chin, Roger (SF) <Roger.Chin@lw.com>; Rip.Finst@thermofisher.com; mpearson@akingump.com; barany@med.cornell.edu; Lumish, Doug (SV) <Doug.Lumish@lw.com>; bjk44@cornell.edu; cnathan@med.cornell.edu
Subject: IPR2016-00557, No. 2035-8 Exhibit - Declaration of Monib Zirvi (P.T.A.B. Nov. 8, 2016)

I was asked by Cornell/ABI and the attorneys to submit this declaration in support of Cornell for the '891 IPR. I would like to submit a similar letter or declaration in support of Cornell in this case. Please let me know how this can be done. I have consulted an attorney who has been very effective against Illumina and his advice is to not trust them and that Jay Flatley has to be "bludgeoned" with the truth for an equitable outcome. He has said that a letter or declaration can be sent even at this late stage as long as all parties are CC'ed. I am fully prepared and willing to submit the declaration independently if absolutely necessary as a non-plaintiff party who has an interest.

Sincerely,

Dr. Monib Zirvi, MD/PhD
Cornell University Medical College, Class of 2000

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Subject Re: Privileged and Confidential: Cornell - Illumina Case; potential obstruction of justice and/or witness tampering; legal team only 6

From Francis Barany <barany@med.cornell.edu>

To: Roger.Chin@lw.com <Roger.Chin@lw.com>

Cc: Matt Pearson <mpearson@akingump.com>, Dianne Elderkin <delderkin@akingump.com>, Douglas Lumish (Doug.Lumish@lw.com) <Doug.Lumish@lw.com>, Gregory.Sobolski@lw.com <Gregory.Sobolski@lw.com>, Finst, Rip <Rip.Finst@thermofisher.com>, Boyle, Sean <sean.boyle@thermofisher.com>, Valerie Cross <vlc1@cornell.edu>, Brian Kelly <bjk44@cornell.edu>, Francis Barany <barany@med.cornell.edu>, Monib Zirvi <matzirvi@yahoo.com>

Date Mar 28, 2017 at 7:59 AM

Dear Roger,

Thank you for your thoughtful analysis of the material we sent, as well as discussing these matters with Matt's team.

I understand that Cornell and ThermoFisher are in discussions to consider their options.

I look forward to helping the team build the strongest case possible.

Best,

Francis

[redacted]

barany@med.cornell.edu

On Mar 27, 2017, at 11:48 PM,
Roger.Chin@lw.com wrote:

PRIVILEGED & CONFIDENTIAL

Francis and Monib,

ECF 1 Exhibit 8

[redacted]

Regards,
Roger

Roger J. Chin

LATHAM & WATKINS LLP
[redacted]

ECF 1 Exhibit 8

From: Francis Barany [mailto:barany@med.cornell.edu]
Sent: Thursday, March 23, 2017 11:58 AM
To: Chin, Roger (SF); Matthew Pearson; Elderkin, Dianne; Lumish, Doug (SV); Sobolski, Gregory (SF); Rip.Finst@thermofisher.com; sean.boyle@thermofisher.com; Valerie Cross; Brian Kelly
Subject: Privileged and Confidential: Cornell - Illumina Case; potential obstruction of justice and/or witness tampering; legal team only 6
Importance: High

Dear Roger, Matthew, Dianne, Doug, Greg, Rip, Sean, Valerie, and Brian,

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

ECF 1 Exhibit 8

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

barany@med.cornell.edu

[redacted]

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Subject Re: IPR2016-00557, Declaration of Monib Zirvi (P.T.A.B. Nov. 8, 2016)

From Valerie Cross Dorn <vlc1@cornell.edu>

To: Monib Zirvi <matzirvi@yahoo.com>

Cc: barany@med.cornell.edu <barany@med.cornell.edu>, sean.boyle@thermofisher.com <sean.boyle@thermofisher.com>, roger.chin@lw.com <roger.chin@lw.com>, Rip.Finst@thermofisher.com <Rip.Finst@thermofisher.com>, Matt Pearson <mpearson@akingump.com>, Doug.Lumish@lw.com <Doug.Lumish@lw.com>, Brian Kelly <bjk44@cornell.edu>, cnathan@med.cornell.edu <cnathan@med.cornell.edu>

Date Mar 31, 2017 at 6:38 PM

PRIVILEGED AND CONFIDENTIAL

Monib, I am sorry it has taken some time to get back to you on this email. While I appreciate your offer to submit a letter or declaration in support of Cornell in this case, there is not an appropriate mechanism to do so at this time so I will defer on your offer. If the need arises I will certainly let you know.

I also wanted to acknowledge that you have every right to hire your own counsel to consult with you, but neither you nor your counsel has Cornell's authorization to file anything in this case on Cornell's behalf. Litigation strategy is coordinated through my office, and those attorneys engaged to represent Cornell's interests. We have been developing a strategy with avid input from you and Francis, and we appreciate your continued support.

Best wishes for a restful weekend,

Valerie

Valerie

Valerie Cross Dorn
Associate University Counsel
Cornell University
[redacted]

On Mar 26, 2017, at 1:57 PM, Monib Zirvi <matzirvi@yahoo.com> wrote:

I was asked by Cornell/ABI and the attorneys to submit this declaration in support of Cornell for the '891 IPR. I would like to submit a similar letter or declaration in support of Cornell in this case. Please let me know how this can be done. I have consulted an attorney who has been very effective against Illumina and his advice is to not trust them and that Jay Flatley has to be "bludgeoned" with the truth for an equitable outcome. He has said that a letter or declaration can be sent even at this late stage as long as all parties are CC'ed. I am fully prepared and willing to submit the declaration independently if absolutely necessary as a non-plaintiff party who has an interest.

Sincerely,

Dr. Monib Zirvi, MD/PhD
Cornell University Medical College, Class of 2000

Sent from my iPhone
<IPR2016-00557, No. 2035-8 Exhibit - Declaration of Monib Zirvi (P.T.A.B. Nov. 8, 2016).pdf>

View less

Subject Re: IPR2016-00557, Declaration of Monib Zirvi (P.T.A.B. Nov. 8, 2016)

From Monib Zirvi <matzirvi@yahoo.com>

To: Valerie Cross Dorn <vlc1@cornell.edu>

Cc: barany@med.cornell.edu <barany@med.cornell.edu>, sean.boyle@thermofisher.com <sean.boyle@thermofisher.com>, roger.chin@lw.com <roger.chin@lw.com>, Rip.Finst@thermofisher.com <Rip.Finst@thermofisher.com>, Matt Pearson <mpearson@akingump.com>, Doug.Lumish@lw.com <Doug.Lumish@lw.com>, Brian Kelly <bjk44@cornell.edu>, cnathan@med.cornell.edu <cnathan@med.cornell.edu>

Date Mar 31, 2017 at 6:49 PM

Dear Valerie,

I appreciate the legal team's efforts and will continue to support Cornell as I have since graduate school as well as in the past 2 years of litigation when called upon to. That being said, if my attorney and I feel that the litigation strategy is not conducive to an equitable outcome for myself or the other inventors, I still reserve the right to act within my rights as advised by my attorney.
I appreciate your understanding in this important matter.

Have a great weekend.

Monib Zirvi
Sent from my iPhone

On Mar 31, 2017, at 6:38 PM, Valerie Cross Dorn <vlc1@cornell.edu> wrote:

PRIVILEGED AND CONFIDENTIAL

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Associate University Counsel
Cornell University
[redacted]

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Cornell University Medical College, Class of 2000

Sent from my iPhone
<IPR2016-00557, No. 2035-8 Exhibit - Declaration of Monib Zirvi (P.T.A.B. Nov. 8, 2016).pdf>

View less

Subject National Academy of Inventors

From Monib Zirvi <matzirvi@yahoo.com>

To: Valerie Cross Dorn
<vlc1@cornell.edu>,
<sean.boyle@thermofisher.com>,
<roger.chin@lw.com>,
<Rip.Finst@thermofisher.com>,
<mpearson@akingump.com>,
<barany@med.cornell.edu>,
<Doug.Lumish@lw.com>,
<bjk44@cornell.edu>,
<cnathan@med.cornell.edu>

Date Apr 8, 2017 at 10:30 PM

Dear All,

I would like to congratulate Francis on being inducted into the National Academy of Inventors. His pioneering work on thermostable ligases, ligase-based detection and Universal Zipcode DNA microarrays was recognized. I'm the legal team can find a way to use this prestigious award (only given thus far to 757 scientists internationally) in their litigation strategy.

http://www.academyofinventors.org/press-releases.asp

All the best,

Monib Zirvi, MD/PhD

Sent from my iPhone

Subject National Academy of Inventors

From Monib Zirvi <matzirvi@yahoo.com>

To: Valerie Cross Dorn
<vlc1@cornell.edu>,
<sean.boyle@thermofisher.com>,
<roger.chin@lw.com>,
<Rip.Finst@thermofisher.com>,
<mpearson@akingump.com>,
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<Doug.Lumish@lw.com>,
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<cnathan@med.cornell.edu>

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http://www.academyofinventors.org/press-releases.asp

All the best,

Monib Zirvi, MD/PhD

Sent from my iPhone

Verizon LTE 1:18 PM 52%
devicechina.com.cn

2016 SPEAKERS

KEYNOTE SPEAKERS

Yubo Fan
President of the School of Biological Science and Medical Engineering
BUAA

Baoting Wang
Deputy Secretary General
CHINA SOCIETY FOR DRUG REGULATION

Dongjin Wang
Former Deputy Minister
MINISTRY OF HUMAN RESOURCES AND SOCIAL SECURITY

SPEAKERS

Kevin Chen
partner at Sequoia Capital
Sequoia Capita

William Cao
President &CEO
YIKON GENOMICS

David Cassak
Managing Partner, Innovation In Medtech, LLC
Innovation In Medtech

Lifei Cheng
Vice President
MEDTRONIC GREATER CHINA

Eli Cohen-Arazi
Rainbow Medical Ltd
Cofounder & Chairman & CEO of Rainbow medical Ltd.

Jian-Bing Fan
Founder and CEO
AnchorDx Corp

Yossi Gross
Co-Founder of Rainbow Medical
Rainbow Medical Ltd

Jian-Bing Fan
Founder and CEO

AnchorDx Corp

Yossi Gross
Co-Founder of Rainbow Medical

Rainbow Medical Ltd

Stephen Levin
Managing Partner, Innovation In Medtech, LLC

Innovation In Medtech

Ning Li
Vice President & Head of Asia Regulatory

SANOFI

Tianping Li
Director of GCP office

THE FIRST AFFILIATED HOSPITAL WITH NANJING MEDICAL UNIVERSITY (JIANGSU PROVINCE HOSPITAL)

Wei Li
Director of Division of Medical Research and Biometric

NATIONAL CENTER FOR CARDIOVASCULAR DISEASES

Xintian Li
Deputy Chief, Medical Device Division

JIANGSU FOOD AND DRUG ADMINISTRATION

shun Lu
professor of Shanghai Chest Hospital

Shanghai Chest Hospital

Sijia Lu
Co-founder and CTO

YIKON GENOMICS

Wenseng Pan
SIDLEY AUSTIN

SIDLEY AUSTIN

Andreas Pfahnl
VP & CTO

Devicix

Jing Qiang
Executive General Manager

China International Capital Corporation Limited

Binghua Su
Professor

College of Basic Medical Sciences, Shanghai Jiao Tong University

Jerry Wang
Head of Market Development, Illumina Greater China

Illumina

Subject RE: National Academy of Inventors

From Doug.Lumish@lw.com
<Doug.Lumish@lw.com>

To: <matzirvi@yahoo.com>,
<vlc1@cornell.edu>,
<sean.boyle@thermofisher.com>,
<Roger.Chin@lw.com>,
<Rip.Finst@thermofisher.com>,
<mpearson@akingump.com>,
<barany@med.cornell.edu>,
<bjk44@cornell.edu>,
<cnathan@med.cornell.edu>

Date Apr 9, 2017 at 3:04 PM

Congratulations, indeed! What a wonderful honor!

-----Original Message-----
From: Monib Zirvi [mailto:matzirvi@yahoo.com]
Sent: Saturday, April 8, 2017 7:31 PM
To: Valerie Cross Dorn <vlc1@cornell.edu>; sean.boyle@thermofisher.com; Chin, Roger (SF) <Roger.Chin@lw.com>; Rip.Finst@thermofisher.com; mpearson@akingump.com; barany@med.cornell.edu; Lumish, Doug (SV) <Doug.Lumish@lw.com>; bjk44@cornell.edu; cnathan@med.cornell.edu
Subject: National Academy of Inventors

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http://www.academyofinventors.org/press-releases.asp

All the best,

Monib Zirvi, MD/PhD

Sent from my iPhone

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Cc: <vlc1@cornell.edu>,
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<mpearson@akingump.com>,
<barany@med.cornell.edu>,
<bjk44@cornell.edu>,
<cnathan@med.cornell.edu>

Date Apr 9, 2017 at 3:52 PM

Hopefully will help the Judge and Jury understand the significance of these research advances developed at Cornell.

Monib

Sent from my iPhone

> On Apr 9, 2017, at 3:04 PM, <Doug.Lumish@lw.com> <Doug.Lumish@lw.com> wrote:
>
> Congratulations, indeed! What a wonderful honor!
>
> -----Original Message-----
> From: Monib Zirvi [mailto:matzirvi@yahoo.com]
> Sent: Saturday, April 8, 2017 7:31 PM
> To: Valerie Cross Dorn <vlc1@cornell.edu>; sean.boyle@thermofisher.com; Chin, Roger (SF) <Roger.Chin@lw.com>; Rip.Finst@thermofisher.com; mpearson@akingump.com; barany@med.cornell.edu; Lumish, Doug (SV) <Doug.Lumish@lw.com>; bjk44@cornell.edu; cnathan@med.cornell.edu
> Subject: National Academy of Inventors
>
> Dear All,

>
> I would like to congratulate Francis on being inducted into the National Academy of Inventors. His

inducted into the National Academy of Inventors. His pioneering work on thermostable ligases, ligase-based detection and Universal Zipcode DNA microarrays was recognized. I'm certain the legal team can find a way to use this prestigious award (only given thus far to 757 scientists internationally) in their litigation strategy.
>
> http://www.academyofinventors.org/press-releases.asp
>
> All the best,
>
> Monib Zirvi, MD/PhD
>
> Sent from my iPhone
> ----------
>
>
> This email may contain material that is confidential, privileged and/or attorney work product for the sole use of the intended recipient. Any review, disclosure, reliance or distribution by others or forwarding without express permission is strictly prohibited. If you are not the intended recipient, please contact the sender and delete all copies including any attachments.
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> Latham & Watkins LLP
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Subject Re: National Academy of Inventors

From Francis Barany
<barany@med.cornell.edu>

To: Doug.Lumish@lw.com
<Doug.Lumish@lw.com>

Cc: Monib Zirvi <matzirvi@yahoo.com>,
Valerie Cross <vlc1@cornell.edu>,
sean.boyle@thermofisher.com
<sean.boyle@thermofisher.com>,
Roger.Chin@lw.com
<Roger.Chin@lw.com>,
Rip.Finst@thermofisher.com
<Rip.Finst@thermofisher.com>,
mpearson@akingump.com
<mpearson@akingump.com>,
bjk44@cornell.edu
<bjk44@cornell.edu>, Carl F. Nathan
<cnathan@med.cornell.edu>

Date Apr 10, 2017 at 8:04 AM

Dear Doug,

Sorry, I was under the weather this weekend, thank you for your kind words, and looking forward to meeting Roger this Wednesday.

Best,

Francis

[redacted]
barany@med.cornell.edu

[redacted]

> On Apr 9, 2017, at 3:04 PM, Doug.Lumish@lw.com
> wrote:
>
> Congratulations, indeed! What a wonderful honor!

Congratulations, indeed! What a wonderful honor!

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To: Valerie Cross Dorn <vlc1@cornell.edu>; sean.boyle@thermofisher.com; Chin, Roger (SF) <Roger.Chin@lw.com>; Rip.Finst@thermofisher.com; mpearson@akingump.com; barany@med.cornell.edu; Lumish, Doug (SV) <Doug.Lumish@lw.com>; bjk44@cornell.edu; cnathan@med.cornell.edu
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https://urldefense.proofpoint.com/v2/url?u=http-3A__www.academyofinventors.org_press-2Dreleases.asp&d=DwIFAg&c=lb62iw4YL4RFalcE2hQUQealT9-RXrryqt9KZX2qu2s&r=wRQkEZLdvrbwX3V1713iXEdsaPTUnWkTvT-Qe4mcOhU&m=viOBJuiWgBAWqRlCOJGu7RdIcPppJcfEIri69PpgpfY&s=_CjKUUaiBfksg87JGEOPsey97uDkrBBjMGbXyilrBJA&e=

All the best,

Monib Zirvi, MD/PhD

Sent from my iPhone

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Latham & Watkins LLP

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Subject CONFIDENTIAL: Conference Call re Settlement of Litigation

From Brian Kelly <bjk44@cornell.edu>

To: Francis Barany <barany@med.cornell.edu>, George Barany <barany@umn.edu>, Bob Hammer <rphammer@gmail.com>, Matthew Lubin <lubingenetics@me.com>, Maria Kempe <maria.kempe@med.lu.se>, Monib Zirvi <matzirvi@yahoo.com>

Cc: Valerie Cross Dorn <vlc1@cornell.edu>, James Kahn <jkahn@med.cornell.edu>, Matt Pearson <mpearson@AKINGUMP.com>

Date Apr 14, 2017 at 9:23 PM

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Please let us know if you are able to participate in the call and we will provide a call in number.

Regards,

Brian

Brian Kelly, Ph.D., CLP

Director, Technology Licensing/WCMC Office

Center for Technology Licensing at Cornell University (CTL)

[redacted]

[redacted]

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Subject Re: CONFIDENTIAL: Conference Call re Settlement of Litigation

From Maria Kempe <maria.kempe@med.lu.se>

To: Brian Kelly <bjk44@cornell.edu>, Francis Barany <barany@med.cornell.edu>, George Barany <barany@umn.edu>, Bob Hammer <rphammer@gmail.com>, Matthew Lubin <lubingenetics@me.com>, Monib Zirvi <matzirvi@yahoo.com>

Cc: Valerie Cross Dorn <vlc1@cornell.edu>, James Kahn <jkahn@med.cornell.edu>, Matt Pearson <mpearson@AKINGUMP.com>

Date Apr 17, 2017 at 4:17 PM

Dear Cornell Associates,

It was with great sadness I read the email message sent at 9:23 pm on Good Friday 2017. The conference call announced in the email message should have taken place BEFORE Cornell made the settlement with Illumina. The fact that it did not is very worrisome and sheds disgrace over Cornell. Incidentally, it is also ironic that the crucifying message was conveyed on a Good Friday. History has shown that crucifixions tend to, sooner or later, backlash with crusades.

From the outcome of this lawsuit and the tone of your email message, I understand that Cornell does not realize the full implications and potentials of these inventions made at the university. I want to remind you that I live and work in Sweden. Sweden is a very small country, but yet every year we assess and award the most important scientific contributions made on earth. In view of my assessment experience, I want to say that you made a very big mistake not letting this lawsuit go to trial to let justice

prevail and the truth come out.

There are many questions around how the lawsuit has

There are many questions around how the lawsuit has been handled by Cornell. From my personal retrospective view, I now wonder why you at all involved me and why you had me to do so much work on your behalf, giving me falsely the impression that you were acting on behalf of my interests. For example, I spent considerable time searching through old documents in my possession, traveled to the US for deposition, provided comments and suggestions on the Markman hearing, and spent several weeks to produce movie clips for the trial. It was therefore very surprising to me that Cornell suddenly agreed on a settlement that gave nothing when there was all to win by going to trial. From my perspective it appears that Cornell was not acting in its own interests, but was dictated in its action by somebody else (ABI or Illumina?). The way this lawsuit has been handled requires an investigation. There seems to be more to this than meets the eye.

I find it questionable that the subject of the email message was labelled with the word “CONFIDENTIAL”. What was confidential in the message? Valerie Cross Dorn declared at several occasions during the past weeks that she declined to answer any questions from me and the other inventors currently not employed by Cornell. I want to remind you that I was working on the invention that was the subject of the lawsuit while I was doing my postdoc at the University of Minnesota more than 20 years ago, financed by two Swedish foundations. I have no confidential obligations towards Cornell, as you are very well aware of. Despite this, during this lawsuit, I have followed all confidential precautions that you and your attorneys have advised on, for the prospect that justice will be reached and the truth will be made public. At this point, you must understand that you have forfeited all my trust and future discretion.

I want to conclude that the way you treat your researchers and inventors is extremely disrespectful and not what I had expected of a university at Cornell’s level. I will inform the foundations that financed my stay in the US on this matter to make sure that they don’t finance and send any future fellows to Cornell. I will also spread the word among colleagues, foundations, and organizations in Sweden and Europe. Not the least my assignments at the European Commission will provide ample opportunities to discuss my distress with colleagues from all over Europe.

Finally, I demand written answers to the questions that I and the other inventors forwarded to Valerie Cross Dorn previously. Only after receiving those answers, I can take part in the announced conference call. At this point, to provide these answers should be seen as an urgent and wise part of Cornell's damage control actions.

Sincerely,
Maria Kempe

From: Brian Kelly <bjk44@cornell.edu>
Sent: Saturday, April 15, 2017 3:23 AM
To: Francis Barany; George Barany; Bob Hammer; Matthew Lubin; Maria Kempe; Monib Zirvi
Cc: Valerie Cross Dorn; James Kahn; Matt Pearson
Subject: CONFIDENTIAL: Conference Call re Settlement of Litigation

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Please let us know if you are able to participate in the call and we will provide a call in number.

Regards,

Brian

Brian Kelly, Ph.D., CLP
Director, Technology Licensing/WCMC Office
Center for Technology Licensing at Cornell University (CTL)

[redacted]

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Subject Re: CONFIDENTIAL: Conference Call re Settlement of Litigation

From Monib Zirvi <matzirvi@yahoo.com>

To: Maria Kempe <maria.kempe@med.lu.se>

Cc: Brian Kelly <bjk44@cornell.edu>, Francis Barany <barany@med.cornell.edu>, George Barany <barany@umn.edu>, Bob Hammer <rphammer@gmail.com>, Matthew Lubin <lubingenetics@me.com>, Valerie Cross Dorn <vlc1@cornell.edu>, James Kahn <jkahn@med.cornell.edu>, Matt Pearson <mpearson@AKINGUMP.com>

Date Apr 17, 2017 at 4:54 PM

I agree with Maria 100 percent. I also refuse to participate in any phone conversation, until written responses to our questions that we had sent are furnished by Cornell as they should have been.

Monib Zirvi

Sent from my iPhone

On Apr 17, 2017, at 4:17 PM, Maria Kempe <maria.kempe@med.lu.se> wrote:

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Please let us know if you are able to participate in the call and we will provide a call in number.

Regards,

Brian

Brian Kelly, Ph.D., CLP
Director, Technology Licensing/WCMC Office
Center for Technology Licensing at Cornell University (CTL)
[redacted]

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Subject Re: CONFIDENTIAL: Conference Call re Settlement of Litigation

From Robert Hammer <rphammer@gmail.com>

To: Brian Kelly <bjk44@cornell.edu>

Cc: Francis Barany <barany@med.cornell.edu>, George Barany <barany@umn.edu>, Matthew Lubin <lubingenetics@me.com>, Maria Kempe <maria.kempe@med.lu.se>, Monib Zirvi <matzirvi@yahoo.com>, Valerie Cross Dorn <vlc1@cornell.edu>, James Kahn <jkahn@med.cornell.edu>, Matt Pearson <mpearson@akingump.com>

Date Apr 17, 2017 at 8:11 PM

Brian:

I agree with many of the sentiments expressed by the other inventors. I feel however it would be valuable to have the discussion this Friday. I plan on joining the conference (as I am taking the day off of work to do so). I think it would also make sense to have the appropriate representatives from the collaborating inventors' institutions (LSU and UMN) present on the call.

Thank you,

Bob

On Fri, Apr 14, 2017 at 9:23 PM, Brian Kelly <bjk44@cornell.edu> wrote:

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Cc: Brian Kelly <bjk44@cornell.edu>, Jim Kahn <jkahn@med.cornell.edu>, Matt Pearson <mpearson@akingump.com>

Date Apr 18, 2017 at 5:18 PM

Dear all:

This email is to acknowledge receipt of the sentiments expressed by Maria, Monib and Bob in response to Brian's message at the bottom of this chain, and to clarify the parameters of the call scheduled for Friday, April 21 at 2:30 Eastern.

This conference call was set up at the specific request of the inventors, for the purpose of answering those questions you posed that we can answer without violating the Protective Order imposed on this case or other constraints of the attorney-client privilege held by Cornell University and ABI/Life as the named plaintiffs in the litigation. In light of the inventors' request to have Matthew Pearson from Akin Gump on the call, we can only include participants who have an attorney-client relationship with Matthew Pearson. Matthew, as you know, represented each of you during the document collection and deposition phase of the case, with your consent and at no expense to you personally, given the alignment of your interests as inventors

with Cornell's interests as the patent owner and named plaintiff in the litigation. He has continued to pursue our collective interests diligently and

pursue our collective interests diligently and thoroughly during the case.

The call was labeled “confidential” because it involves a discussion of information that is not public. For example, one of your questions deals with what rights Cornell has under the New Exclusive License Agreement entered with Life in 2009 (under which Life agreed to and has paid the multi-million dollar legal expenses associated with this case). Several of your questions deal with guidance you received during the deposition phase. If you no longer wish to receive answers to the questions you posed, and if you are unable to commit to treating the information we provide during the call as confidential, please let me know and we will reevaluate the need for the call. Dial-in information will be forthcoming after we know who has agreed to participate in the call.

I encourage each of you to participate in the call, and I believe Francis Barany and Brian Kelly join me in in the hope that, by participating on Friday, you will have a better understanding of the case and its outcome.

Valerie Cross Dorn
Associate University Counsel
Cornell University
[redacted]

> On Apr 17, 2017, at 8:10 PM, Robert Hammer <rphammer@gmail.com> wrote:
>
> Brian:
>
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Brian

Brian Kelly, Ph.D., CLP
Director, Technology Licensing/WCMC Office
Center for Technology Licensing at Cornell University (CTL)

Center for Technology Licensing at Cornell University (CTL)

[redacted]

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Subject Re: Daily News: Illumina, Cornell Dismiss Patent Dispute

From Francis Barany <barany@med.cornell.edu>

To: Valerie Cross <vlc1@cornell.edu>, James R. Kahn <jkahn@med.cornell.edu>, Brian Kelly <bjk44@cornell.edu>, Matt Pearson <mpearson@AKINGUMP.com>

Cc: George Barany <barany@umn.edu>, Robert Hammer <rphammer@gmail.com>, Monib Zirvi <matzirvi@yahoo.com>, lubingenetics@me.com <lubingenetics@me.com>, Maria Kempe <maria.kempe@med.lu.se>, Goldman Mike <Michael.Goldman@leclairryan.com>, Carl F. Nathan <cnathan@med.cornell.edu>

Date Apr 19, 2017 at 4:09 PM

Dear Team,

Headline from GenomeWeb today. See below.

We are still awaiting details for the call in on Friday @ 2:30.

Best,

Francis

[redacted]
barany@med.cornell.edu

[redacted]

Illumina, Cornell Dismiss Patent Dispute

Apr 19, 2017 | staff reporter

NEW YORK (GenomeWeb) – Illumina and Cornell University have jointly agreed to dismiss a patent dispute that originated in 2010, according to documents filed with the US District Court for the District of Delaware.

Cornell and Life Technologies (now part of Thermo Fisher Scientific) sued Illumina in May 2010, claiming that Illumina's microarray products infringed on eight patents held by Cornell and exclusively licensed to Life Tech.

The patents related to claims on detecting nucleic acid sequences using coupled ligase detection and PCR. In May 2016, the court

issued recommendations for claims reconstruction, and then partly adopted and partly rejected those recommendations in January, following comments by both parties.

This week, both parties sought to have those prior rulings withdrawn. Cornell and Life Technologies agreed to dismiss their claims against Illumina "with prejudice," and Illumina agreed to dismiss its counterclaims "without prejudice." Each party also agreed to cover its own legal costs. The court subsequently vacated its prior claims reconstruction recommendation and order.

Begin forwarded message:

From: GenomeWeb <newsletters@genomeweb.com>
Subject: Daily News: Illumina, Cornell Dismiss Patent Dispute
Date: April 19, 2017 at 4:01:51 PM EDT
To: <barany@med.cornell.edu>
Reply-To: <newsletters@genomeweb.com>

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Daily News

The Latest Headlines from the GenomeWeb Newsroom

Breaking News

Illumina, Cornell Dismiss Patent Dispute

Cornell and Life Technologies sued Illumina in 2010, alleging Illumina's microarray products infringed on eight of their patents. Read more >

MeMed Awarded $9.2M DoD Contract

The funding will go toward completing the development of the company's point-of-care platform for distinguishing bacterial from viral infections. Read more >

Synpromics Raises £5.2M

The company intends to use a portion of the funding to further develop its PromPT synthetic promoter design platform. Read more >

ThermaGenix Completes $1.5M Series A-1

Financing

The funds will be used in part to support commercial activities related to the firm's ThermaStop and ThermaGo PCR additive reagents. Read more >

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The new algorithm, called TOPSPIN, complements the company's MMprofiler test. It is considering making TOPSPIN-generated data available to its MMprofiler patients. Read more >

Qiagen GeneReader Users Present Early Results at AMP Global Congress

Groups from Austria, Spain, Germany, and the US demonstrated that the GeneReader can reliably detect cancer mutations in tissue and liquid biopsy samples. Read more >

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Daily News

The Latest Headlines from the GenomeWeb Newsroom

Breaking News

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Subject 2nd Principal Investigators Meeting Abstracts

From Monib Zirvi <matzirvi@yahoo.com>

To: <barany@med.cornell.edu>

Cc: <Rip.Finst@thermofisher.com>, Matthew Pearson <mpearson@akingump.com>, <roger.chin@lw.com>, Valerie Cross Dorn <vlc1@cornell.edu>, <sean.boyle@thermofisher.com>, <barany@med.cornell.edu>, <Doug.Lumish@lw.com>, <bjk44@cornell.edu>

Date Mar 18, 2017 at 11:12 AM

Look at Fu's abstract

Xiang-Dong Fu

University of California, San Diego

Cancer Classification Based on MRNA Isoforms

Xiang-Dong Fu[1], Joanne M. Yeakley[1], Jian-Bing Fan[2], Mark Chee[2], David Tarin[3], Michael Gribskov[4], and Michael Zhang[5]

[1]Department of Cellular and Molecular Medicine, University of California, San Diego, [2]Illumina, Inc., San Diego,[3]UCSD Cancer Center, [4]San Diego Supercomputer Center, and [5]Cold Spring Harbor Laboratory

Recent completion of the human genome project has set the stage for understanding network regulation of gene expression in biology. One of the major surprises is the large number of mRNA isoforms generated by alternative splicing (60% of human genes express more than one transcript and this percentage is likely underestimated), which

undoubtedly contributes to molecular diversity in complex biological pathways. In our battle against cancer, variations in mRNA isoforms may underlie

cancer, variations in mRNA isoforms may underlie many previously unrecognized mechanisms for cellular transformation, and therefore may prove valuable for cancer diagnosis and characterization of potential therapeutic targets.

Our project aims at developing a genomic approach to alternative splicing because current techniques for assaying alternative splicing rely on low throughput methods that are not suitable for genome-wide analysis. The technology utilizes the addressable zip- code strategy on fiber optic-based microarrays developed at Illumina. Briefly, DNA oligos are used to cover specific splice junction sequences and each isoform-sepcific oligo is linked to a unique zip-code sequence. The oligos are first hybridized to total RNA and those detecting specific alternative splicing events are selectively amplified by PCR. Individual splicing events are then sorted and quantified on a universal Zipcode array. Using this novel microarray technology, we can detect specific alternative splicing events with unprecedented specificity and sensitivity, reaching to the single cell level in certain cases. Furthermore, semi-quantitative data are obtained from a panel of experimental cell lines and 90% of data points match the results obtained by conventional RT-PCR. Although we have been focusing on technology development in the initial R21 phase, our research has already led to the discovery of a number of striking cell-specific alternative splicing events in our model systems.

In the future, we plan to refine the assay to determine optimal experimental conditions for large scale application of the technology. We are interested in coupling our technology with sample preparation methods, such as immunofractionation of cells and laser capture microscopy. This will allow us to analyze alternative splicing in cell populations associated with distinct cancer stages. In particular, we plan to examine several hundred prostate cancer samples available at the UCSD Cancer Center to

explore the utility of variations in alternative splicing for cancer classification. Parallel to our experimental efforts, our collaborators on the team will develop computational tools to aid database construction and analysis.

Sent from my iPhone

2nd Principal Investigators Meeting Abs…

Subject Re: Daily News: Illumina, Cornell Dismiss Patent Dispute

From Francis Barany <barany@med.cornell.edu>

To: Valerie Cross <vlc1@cornell.edu>, James R. Kahn <jkahn@med.cornell.edu>, Brian Kelly <bjk44@cornell.edu>, Matt Pearson <mpearson@AKINGUMP.com>

Cc: George Barany <barany@umn.edu>, Robert Hammer <rphammer@gmail.com>, Monib Zirvi <matzirvi@yahoo.com>, lubingenetics@me.com <lubingenetics@me.com>, Maria Kempe <maria.kempe@med.lu.se>, Michael Goldman <Michael.Goldman@leclairryan.com>, Carl F. Nathan <cnathan@med.cornell.edu>

Date Apr 20, 2017 at 8:09 AM

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Date Apr 20, 2017 at 9:50 AM

Dear All,

I previously responded to Brian Kelly's Friday e-mail, indicating that I would like to participate. I appreciate everyone's efforts and thoughtfulness at this challenging juncture.

GB

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Daily News

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Breaking News

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George Barany
Distinguished McKnight University Professor of Chemistry
University of Minnesota
Department of Chemistry
[redacted]

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From Monib Zirvi <matzirvi@yahoo.com>

To: Valerie Cross Dorn <vlc1@cornell.edu>

Cc: Francis Barany <barany@med.cornell.edu>, Jim Kahn <jkahn@med.cornell.edu>, Brian Kelly <bjk44@cornell.edu>, Matt Pearson <mpearson@AKINGUMP.com>, George Barany <barany@umn.edu>, Robert Hammer <rphammer@gmail.com>, lubingenetics@me.com <lubingenetics@me.com>, Maria Kempe <maria.kempe@med.lu.se>, Michael Goldman <Michael.Goldman@leclairryan.com>, Carl F. Nathan <cnathan@med.cornell.edu>

Date Apr 20, 2017 at 9:51 AM

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Sent from my iPhone

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Date Apr 20, 2017 at 9:52 AM

Dear Valerie,

I do believe that George had sent an earlier email indicating his interest in the conference call. You may not have been copied on this correspondence, so I am re-pasting it into the email below.

Valerie, I politely suggest that the dial-in number be circulated to all the inventors, and they can decide on their availability to participate. Some of the material in the email below are relevant to those copied on this email — so in the interest of full transparency, they were included, but I do understand if you want to limit this particular call to just Cornell legal team, Matthew, and the inventors.

As mentioned below, the inventors have also requested that I represent them in a discussion about Cornell's next steps forward (which we believe should include both Carl Nathan and Mike Goldman).

Thank you for your good-faith willingness to help explain Cornell's perspective and rational for making these difficult decisions.

Best,

Francis

[redacted]
barany@med.cornell.edu

[redacted]

———————

Dear Brian,

I appreciate all of the hard work by you and the team on this, and will be interested in learning more at the conference call. Please let me know what number to call in to.

Best wishes,

GB
--
George Barany
Distinguished McKnight University Professor of Chemistry
University of Minnesota
Department of Chemistry
[redacted]

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Date Apr 20, 2017 at 10:17 AM

I will join.

I want add the following questions to the list of questions:

(1) Did the settlement result in any damage to be paid by Illumina? Who will receive such a damage?

(2) Will Cornell receive any other benefits apart from monetary ones from the settlement? Will ABI receive any other benefits apart from monetary ones from the settlement?

(3) Why did Cornell decide to do a settlement at this point?

(4) How will Cornell handle the PR and press around this? A number of news agencies around the world has already released notes about this and more notes are steadily appearing. Soon there will be speculations about the outcome of the settlement. The conclusions everybody can draw from the press notes so far are that either (a) a damage will be paid by Illumina to Cornell or (b) there was no ground for Cornell suing Illumina in the first round and 7 years of lawsuit has showed that there was no infringement and Cornell decided/was forced to give in. Alternative (b) backlashes greatly on inventors. What will Cornell do to protect inventors' reputation?

Maria

From: Monib Zirvi <matzirvi@yahoo.com>

Sent: Thursday, April 20, 2017 3:51 PM
To: Valerie Cross Dorn
Cc: Francis Barany; Jim Kahn; Brian Kelly; Matt Pearson; George Barany; Robert Hammer; lubingenetics@me.com; Maria Kempe; Michael Goldman; Carl F. Nathan
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Presenters highlighted early work that supports the push for a national, systematic effort to elucidate progression from precancerous states to clinical malignancy. Read more >

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Research Associate

Company: New England Research Institutes (NERI)
Location: Watertown MA

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Company: Precision NanoSystems, Inc.
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Subject Re: CONFIDENTIAL: Conference Call re Settlement of Litigation

From Valerie Cross Dorn <vlc1@cornell.edu>

To: Francis Barany <barany@med.cornell.edu>

Cc: Jim Kahn <jkahn@med.cornell.edu>, Brian Kelly <bjk44@cornell.edu>, Matt Pearson <mpearson@AKINGUMP.com>, George Barany <barany@umn.edu>, Robert Hammer <rphammer@gmail.com>, Monib Zirvi <matzirvi@yahoo.com>, lubingenetics@me.com <lubingenetics@me.com>, Maria Kempe <maria.kempe@med.lu.se>, Michael Goldman <Michael.Goldman@leclairryan.com>, Carl F. Nathan <cnathan@med.cornell.edu>

Date Apr 20, 2017 at 6:38 PM

Francis, I have already explained to you and the other inventors why this call on Friday is being restricted to the inventors who were represented by Akin Gump during their participation in document collection and depositions for the case, based on the inventors' specific request to speak with Matthew.

I asked for a commitment from those who are interested in participating in the discussion that was requested, under the confidential legend the invitation contained. You noted in an email yesterday at 11:45 a.m. that email is not the best form of communication and respectfully suggested that everyone participate in the call on Friday to hear the information we are able to share. Yet emails continue to circulate among you, making assertions without information other than what you have read in news reports, and those who declined the confidentiality request have not altered their positions, at least not as far as I can discern in the multiple emails sent since last Friday night. Please understand that there is no "full transparency" that applies when an attorney-client privilege applies.

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proceed to discuss issues amongst yourselves.

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I do have a conference line arranged and will forward it upon your clarification, under the guidance outlined in this email, and omit Mike Goldman and Carl Nathan. Thank you,

Valerie Cross Dorn
Associate University Counsel

Associate University Counsel
Cornell University
[redacted]

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<barany@med.cornell.edu> wrote:

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Valerie, I politely suggest that the dial-in number be circulated to all the inventors, and they can decide on their availability to participate. Some of the material in the email below are relevant to those copied on this email — so in the interest of full transparency, they were included, but I do understand if you want to limit this particular call to just Cornell legal team, Matthew, and the inventors.

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[redacted]
barany@med.cornell.edu

[redacted]

———————
Dear Brian,

I appreciate all of the hard work by you and the team on this, and will be interested in learning more at the conference call. Please let me know what number to call in to.

Best wishes,

GB
--
George Barany
Distinguished McKnight University Professor of Chemistry
University of Minnesota
Department of Chemistry
[redacted]

[redacted]

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Inventors: Would you please review questions to make sure those that are important to you are still included?

Inventors: Would you please add if any questions are missing?

Cornell members: Would you want me to set up a webex, or will you do so?

Cornell members: There are additional questions about next steps forward that would not include Matthew Pearson. The inventors have asked that I represent them, and set up a meeting after the Friday meeting to discuss.

Thank you all, and looking forward to the discussion on Friday @ 2:30 PM EDT.

Best,

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[redacted]
barany@med.cornell.edu

[redacted]

———————————————

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application US20030096239, Illumina tried to re-patent 16 of our zipcodes? (As we have previously discussed, FB and MZ did not learn the full extent of Illumina's conduct until August of 2015).

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20. The terms of the agreement state: "Cornell and Life Technologies agreed to dismiss their claims against Illumina "with prejudice," and Illumina agreed to dismiss its counterclaims "without prejudice." " What does that mean? How does that benefit Cornell?

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1. Were the Board of Cornell University and Weill Cornell Medicine given a full picture of what was at stake during the settlement discussion? How come the inventors could not weigh in at that meeting, if there ever was one?

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5. Has the Judge finalized the settlement, and if not can we intercede as non-plaintiff parties who have an interest?

On Apr 19, 2017, at 4:09 PM, Francis Barany <barany@med.cornell.edu> wrote:

Dear Team,

Headline from GenomeWeb today. See below.

We are still awaiting details for the call in on Friday @ 2:30.

Best,

Francis

[redacted]

barany@med.cornell.edu

[redacted]

Illumina, Cornell Dismiss Patent Dispute

Apr 19, 2017 | staff reporter

NEW YORK (GenomeWeb) – Illumina and Cornell University have jointly agreed to dismiss a patent dispute that originated in 2010, according to documents filed with the US District Court for the District of Delaware.

Cornell and Life Technologies (now part of Thermo Fisher Scientific) sued Illumina in May 2010, claiming that Illumina's microarray products infringed on eight patents held by Cornell and exclusively licensed to Life Tech.

The patents related to claims on detecting nucleic acid sequences using coupled ligase detection and PCR. In May 2016, the court issued recommendations for claims reconstruction, and then partly adopted and partly rejected those recommendations in January, following comments by both parties.

This week, both parties sought to have those prior rulings withdrawn.

Cornell and Life Technologies agreed to dismiss their claims against Illumina "with prejudice," and Illumina agreed to dismiss its counterclaims "without prejudice." Each party also agreed to cover its own legal costs. The court subsequently vacated its prior claims reconstruction recommendation and order.

Begin forwarded message:

From: GenomeWeb <newsletters@genomeweb.com>
Subject: Daily News: Illumina, Cornell Dismiss Patent Dispute
Date: April 19, 2017 at 4:01:51 PM EDT
To: <barany@med.cornell.edu>
Reply-To: <newsletters@genomeweb.com>

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Illumina, Cornell Dismiss Patent Dispute

Cornell and Life Technologies sued Illumina in 2010, alleging Illumina's microarray products infringed on eight of their patents. Read more >

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The funding will go toward completing the development of the company's point-of-care platform for distinguishing bacterial from viral infections. Read more >

Synpromics Raises £5.2M

The company intends to use a portion of the funding to further develop its PromPT synthetic promoter design platform. Read more >

ThermaGenix Completes $1.5M Series A-1 Financing

The funds will be used in part to support commercial activities related to the firm's ThermaStop and ThermaGo PCR additive reagents. Read more >

Tissue-Specific Transcriptome Used to Enhance Exome-, Genome-Based Dystrophy Diagnoses

Incorporating splicing and other clues from muscle transcripts, researchers reached diagnoses in cases that were inconclusive after sequencing alone. Read more >

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Laboratory Director

Laboratory Director

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Location: Salt Lake City UT

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Director of Research and Development

Company: Bioreference Location: Elmwood Park NJ

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Subject Re: CONFIDENTIAL: Conference Call re Settlement of Litigation

From George Barany <barany@umn.edu>

To: Valerie Cross Dorn <vlc1@cornell.edu>

Cc: Francis Barany <barany@med.cornell.edu>, Jim Kahn <jkahn@med.cornell.edu>, Brian Kelly <bjk44@cornell.edu>, Matt Pearson <mpearson@akingump.com>, Robert Hammer <rphammer@gmail.com>, Monib Zirvi <matzirvi@yahoo.com>, lubingenetics@me.com <lubingenetics@me.com>, Maria Kempe <maria.kempe@med.lu.se>, Michael Goldman <Michael.Goldman@leclairryan.com>, Carl F. Nathan <cnathan@med.cornell.edu>

Date Apr 20, 2017 at 6:54 PM

Dear All,

Writing just for myself, I believe it would be very useful to proceed at the suggested time tomorrow, under the terms outlined by Valerie Cross Dorn (and conveyed in Brian Kelly's Friday e-mail). I commit to keeping confidential anything that is learned, particularly to the extent that information may be forthcoming that differs from what has been reported publicly. Several of us have already made appropriate arrangements with our schedules.

I also appreciate Valerie's invitation (if I'm reading the e-mail correctly) for further dialogue that does not involve Matthew Pearson, and that may (or may not) involve Carl Nathan and/or Mike Goldman. I trust Francis and Valerie to work together on such an agenda, but in the meantime, let's move forward with tomorrow's call.

Best wishes,

GB

On Thu, Apr 20, 2017 at 5:37 PM, Valerie Cross Dorn <vlc1@cornell.edu> wrote:

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Cornell University
[redacted]

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[redacted]

[redacted]
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Department of Chemistry
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From: GenomeWeb <newsletters@genomeweb.com>
Subject: Daily News: Illumina, Cornell Dismiss Patent Dispute
Date: April 19, 2017 at 4:01:51 PM EDT
To: <barany@med.cornell.edu>
Reply-To: <newsletters@genomeweb.com>

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--
George Barany
Distinguished McKnight University Professor of Chemistry
University of Minnesota
Department of Chemistry
[redacted]

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Date Apr 20, 2017 at 7:50 PM

Dear Valerie,

I agree with George, please send out the call information.

Please invite Matthew and all the inventors.

Thanks, and looking forward to the discussion tomorrow.

Best,

Francis

Sent from my iPhone

On Apr 20, 2017, at 6:54 PM, George Barany <barany@umn.edu> wrote:

> Dear All,
>
> Writing just for myself, I believe it would be very useful to proceed at the suggested time tomorrow, under the terms outlined by Valerie Cross Dorn (and conveyed in Brian Kelly's Friday e-mail). I commit to keeping confidential anything that is learned, particularly to the extent that information may be forthcoming that differs from what has been reported publicly. Several of us have already made
>
> appropriate arrangements with our schedules.
>
> I also appreciate Valerie's invitation (if I'm reading the e-mail correctly) for further dialogue that does not involve Matthew Pearson, and that may (or may not) involve Carl Nathan and/or Mike Goldman. I trust Francis and Valerie to work together on such an agenda, but in the meantime, let's move forward with tomorrow's call.
>
> Best wishes,
>
> GB
>
> On Thu, Apr 20, 2017 at 5:37 PM, Valerie Cross Dorn <vlc1@cornell.edu> wrote:
>
> > Francis, I have already explained to you and the other inventors

why this call on Friday is being restricted to the inventors who were represented by Akin Gump during their participation in document collection and depositions for the case, based on the inventors' specific request to speak with Matthew.

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I do have a conference line arranged and will forward it upon your clarification, under the guidance outlined in this email, and omit Mike Goldman and Carl Nathan. Thank you,

Valerie Cross Dorn
Associate University Counsel
Cornell University
[redacted]

On Apr 20, 2017, at 9:52 AM, Francis Barany <barany@med.cornell.edu> wrote:

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Valerie, I politely suggest that the dial-in number be circulated to all the inventors, and they can decide on their availability to participate. Some of the material in the email below are relevant to those copied on this email — so in the interest of full transparency, they were included, but I do understand if you want to limit this particular call to just Cornell legal team, Matthew, and

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As mentioned below, the inventors have also requested that I represent them in a discussion about Cornell's next steps forward (which we believe should include both Carl Nathan and Mike Goldman).

Thank you for your good-faith willingness to help explain Cornell's perspective and rational for making these difficult decisions.

Best,

Francis

[redacted]
barany@med.cornell.edu

[redacted]

———————
Dear Brian,

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Best wishes,

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Distinguished McKnight University Professor of Chemistry
University of Minnesota
Department of Chemistry
[redacted]

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as some new questions about the "without prejudice vs. with prejudice." clause.

Inventors: Would you please review questions to make sure those that are important to you are still included?

Inventors: Would you please add if any questions are missing?

Cornell members: Would you want me to set up a webex, or will you do so?

Cornell members: There are additional questions about next steps forward that would not include Matthew Pearson. The inventors have asked that I represent them, and set up a meeting after the Friday meeting to discuss.

Thank you all, and looking forward to the discussion on Friday @ 2:30 PM EDT.

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Francis

[redacted]
barany@med.cornell.edu

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———————————————

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6B. When did Cornell first learn that within Illumina patent application US20030096239, Illumina tried to re-patent 16 of our zipcodes? (As we have previously discussed, FB and MZ did not learn the full extent of Illumina's conduct until August of 2015).

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17A. What other demands has Illumina made as part of the settlement talks that have been initiated?

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inventors so that we can pursue other options?

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20. The terms of the agreement state: "Cornell and Life Technologies agreed to dismiss their claims against Illumina "with prejudice," and Illumina agreed to dismiss its counterclaims "without prejudice." " What does that mean? How does that benefit Cornell?

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The following additional questions were put forth by Monib:

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5. Has the Judge finalized the settlement, and if not can we intercede as non-plaintiff parties who have an interest?

On Apr 19, 2017, at 4:09 PM, Francis Barany

<barany@med.cornell.edu> wrote:

Dear Team,

Headline from GenomeWeb today. See below.

We are still awaiting details for the call in on Friday @ 2:30.

Best,

Francis

[redacted]
barany@med.cornell.edu

[redacted]

Illumina, Cornell Dismiss Patent Dispute

Apr 19, 2017 | staff reporter

NEW YORK (GenomeWeb) – Illumina and Cornell University have jointly agreed to dismiss a patent dispute that originated in 2010, according to documents filed with the US District Court for the District of Delaware.

Cornell and Life Technologies (now part of Thermo Fisher Scientific) sued Illumina in May 2010, claiming that Illumina's microarray products infringed on eight patents held by Cornell and exclusively licensed to Life Tech.

The patents related to claims on detecting nucleic acid sequences using coupled ligase detection and PCR. In May 2016, the court issued recommendations for claims reconstruction, and then partly adopted and partly rejected those recommendations in January, following comments by both parties.

This week, both parties sought to have those prior rulings withdrawn. Cornell and Life Technologies agreed to dismiss their claims against Illumina "with prejudice," and Illumina agreed to dismiss its counterclaims "without prejudice." Each party also agreed to cover its

own legal costs. The court subsequently vacated its prior claims reconstruction recommendation and order.

Begin forwarded message:

From: GenomeWeb <newsletters@genomeweb.com>
Subject: Daily News: Illumina, Cornell Dismiss Patent Dispute
Date: April 19, 2017 at 4:01:51 PM EDT
To: <barany@med.cornell.edu>
Reply-To: <newsletters@genomeweb.com>

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Daily News

The Latest Headlines from the GenomeWeb Newsroom

Breaking News

Illumina, Cornell Dismiss Patent Dispute
Cornell and Life Technologies sued Illumina in 2010, alleging Illumina's microarray products infringed on eight of their patents. Read more >

MeMed Awarded $9.2M DoD Contract
The funding will go toward completing the development of the company's point-of-care platform for distinguishing bacterial from viral infections. Read more >

Synpromics Raises £5.2M
The company intends to use a portion of the funding to further develop its PromPT synthetic promoter design platform. Read more >

ThermaGenix Completes $1.5M Series A-1 Financing
The funds will be used in part to support commercial activities related to the firm's ThermaStop and ThermaGo PCR additive reagents. Read more >

Tissue-Specific Transcriptome Used to Enhance Exome-, Genome-Based Dystrophy Diagnoses
Incorporating splicing and other clues from muscle transcripts, researchers reached diagnoses in cases that were inconclusive after sequencing alone. Read more >

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AACR Speakers Make Case for Pre-Cancer Genome Atlas as Early Detection Technologies Loom
Presenters highlighted early work that supports the push for a national, systematic effort to elucidate progression from precancerous states to clinical malignancy. Read more >

SkylineDx Develops Tool to Predict Cancer Therapies Based on Genomic Data
The new algorithm, called TOPSPIN, complements the company's MMprofiler test. It is considering making TOPSPIN-generated data available to its MMprofiler patients. Read more >

Qiagen GeneReader Users Present Early

Results at AMP Global Congress

Groups from Austria, Spain, Germany, and the US demonstrated that the GeneReader can reliably detect cancer mutations in tissue and liquid biopsy samples. Read more >

DNAlytics, VIB Partner to Develop Colorectal Cancer Screening Test

The blood-based test will use a 23-gene expression signature identified by researchers at VIB-KU Leuven and their collaborators. Read more >

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Biodesix Banking on Rapid Turnaround Time to Drive Adoption of GeneStrat NSCLC Test

According to a new study, the company returns results for more than 90 percent of its GeneStrat tests within 72 hours and aims to bring that down to 48 hours.

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Two Groups Evaluating BRCA1/2 Variant Discrepancies in Public Database at Odds Over Patient Impact

One paper involving experts from Myriad Genetics and another from Invitae added fresh data to a contentious debate over the use of public variant databases.

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Nanobiosym EUA Zika Test Part of Expanding Menu Intended for Point-of-Care

The test was approved for lab use, but it runs on a platform with the potential for point-of-care applications.

Read more

Premium

Though Most Liquid Biopsy Tests Are LDTs, Stakeholders Continue to Weigh Regulatory Considerations

At the AACR annual meeting earlier this month, attendees discussed challenges in demonstrating analytical and clinical validity appropriately for liquid biopsy tests.

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Research Associate
Company: New England Research Institutes (NERI)
Location: Watertown MA

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Field Application Scientist - Western North America
Company: Precision NanoSystems, Inc.
Location: South San Francisco CA

Apply now

Laboratory Director
Company: NAViCAN Genomics, Inc.
Location: Salt Lake City UT

Apply now

Director of Research and Development
Company: Bioreference Location: Elmwood Park NJ

Apply now

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--
George Barany
Distinguished McKnight University Professor of Chemistry
University of Minnesota
Department of Chemistry
[redacted]

[redacted]

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Subject Re: CONFIDENTIAL: Conference Call re Settlement of Litigation

From Monib Zirvi <matzirvi@yahoo.com>

To: Valerie Cross Dorn <vlc1@cornell.edu>

Cc: Francis Barany <barany@med.cornell.edu>, Jim Kahn <jkahn@med.cornell.edu>, Brian Kelly <bjk44@cornell.edu>, Matt Pearson <mpearson@AKINGUMP.com>, George Barany <barany@umn.edu>, Robert Hammer <rphammer@gmail.com>, lubingenetics@me.com <lubingenetics@me.com>, Maria Kempe <maria.kempe@med.lu.se>, Michael Goldman <Michael.Goldman@leclairryan.com>, Carl F. Nathan <cnathan@med.cornell.edu>

Date Apr 20, 2017 at 8:53 PM

If the settlement we are discussing tomorrow is already a done deal, why is Judge Stark asking for a teleconference on Monday to discuss stipulations?

Nature of Suit 830 Patent

Last Update: 22 hours ago. Update

Filing Date #	Docket Text
4/19/2017 597	ORAL ORDER: IT IS HEREBY ORDERED that the Court will hold a teleconference on Monday, April 24 at 10:00 a.m. to discuss the proposed stipulations. Counsel for Plaintiffs shall initiate the call to (302) 573-4573. ORDERED by Judge Leonard P. Stark on 4/19/17. (ntl) (Entered: 04/19/2017)
4/18/2017	Joint STIPULATION to Dismiss (and

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From: GenomeWeb <newsletters@genomeweb.com>
Subject: Daily News: Illumina, Cornell Dismiss Patent Dispute
Date: April 19, 2017 at 4:01:51 PM EDT
To: <barany@med.cornell.edu>
Reply-To: <newsletters@genomeweb.com>

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Daily News

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Breaking News

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Nanobiosym EUA Zika Test Part of Expanding Menu Intended for Point-of-Care

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Company: New England Research Institutes (NERI)

Location: Watertown MA

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Field Application Scientist - Western North America

Company: Precision NanoSystems, Inc.
Location: South San Francisco CA

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Laboratory Director

Company: NAViCAN Genomics, Inc.
Location: Salt Lake City UT

Apply now

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Company: Bioreference Location: Elmwood Park NJ

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Subject Re: CONFIDENTIAL: Conference Call re Settlement of Litigation

From Maria Kempe <maria.kempe@med.lu.se>

To: Valerie Cross Dorn <vlc1@cornell.edu>

Cc: Francis Barany <barany@med.cornell.edu>, Jim Kahn <jkahn@med.cornell.edu>, Brian Kelly <bjk44@cornell.edu>, Matt Pearson <mpearson@AKINGUMP.com>, George Barany <barany@umn.edu>, Robert Hammer <rphammer@gmail.com>, Monib Zirvi <matzirvi@yahoo.com>, lubingenetics@me.com <lubingenetics@me.com>, Michael Goldman <Michael.Goldman@leclairryan.com>, Carl F. Nathan <cnathan@med.cornell.edu>

Date Apr 21, 2017 at 9:17 AM

Of course I want information on what is going on. Presently, I have obtained more details
from Reuters journalists and other documents publicly available online than from Cornell
representatives. This situation is highly unsatisfactory. To the extent Matthew Pearson
will reveal any more information that is not already, or will not be, publicly known, I will
acknowledge the client attorney privilige.

Maria

Sent from my iPad

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barany@med.cornell.edu

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University of Minnesota
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Apr 19, 2017 | staff reporter

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Begin forwarded message:

From: GenomeWeb <newsletters@genomeweb.com>
Subject: Daily News: Illumina, Cornell Dismiss Patent Dispute
Date: April 19, 2017 at 4:01:51 PM EDT
To: <barany@med.cornell.edu>
Reply-To: <newsletters@genomeweb.com>

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Daily News

The Latest Headlines from the GenomeWeb Newsroom

Breaking News

Illumina, Cornell Dismiss Patent Dispute

Cornell and Life Technologies sued Illumina in 2010

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One paper involving experts from Myriad Genetics and another from Invitae added fresh data to a contentious debate over the use of public variant databases.

Read more

Premium

Nanobiosym EUA Zika Test Part of Expanding Menu Intended for Point-of-Care

The test was approved for lab use, but it runs on a platform with the potential for point-of-care applications.

Read more

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Location: Watertown MA

Apply now

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Location: South San Francisco CA

Apply now

Laboratory Director

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Apply now

Director of Research and Development

Company: Bioreference Location: Elmwood Park NJ

Apply now

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Subject Re: CONFIDENTIAL: Dial-in Information for Conference Call re Settlement of Litigation

From Valerie Cross Dorn <vlc1@cornell.edu>

To: Francis Barany <barany@med.cornell.edu>, George Barany <barany@umn.edu>, Robert Hammer <rphammer@gmail.com>, lubingenetics@me.com <lubingenetics@me.com>, Monib Zirvi <matzirvi@yahoo.com>, Maria Kempe <maria.kempe@med.lu.se>

Cc: Jim Kahn <jkahn@med.cornell.edu>, Brian Kelly <bjk44@cornell.edu>, Matt Pearson <mpearson@akingump.com>

Date Apr 21, 2017 at 11:02 AM

Here is the teleconference information for today's call at 2:30 Eastern Time (international dial-in included) to discuss settlement of the case against Illumina:

Dial-in Number (U.S. & Canada)
[redacted]

International Dial-in Number
[redacted]

Conference Code
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Security Passcode
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Writing just for myself, I believe it would be very useful to proceed at the suggested time tomorrow, under the terms outlined by Valerie Cross Dorn (and conveyed in Brian Kelly's Friday e-mail). I commit to keeping confidential anything that is learned, particularly to the extent that information may be forthcoming that differs from what has been reported publicly. Several of us have already made appropriate arrangements with our schedules.

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Subject: Daily News: Illumina, Cornell Dismiss Patent Dispute
Date: April 19, 2017 at 4:01:51 PM EDT
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Reply-To: <newsletters@genomeweb.com>

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Breaking News

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Laboratory Director

Company: NAViCAN Genomics, Inc.
Location: Salt Lake City UT

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Director of Research and Development

Company: Bioreference Location: Elmwood Park NJ

Apply now

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George Barany
Distinguished McKnight University Professor of Chemistry
University of Minnesota
Department of Chemistry
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Subject Re: CONFIDENTIAL: Dial-in Information for Conference Call re Settlement of Litigation

From Monib Zirvi <matzirvi@yahoo.com>

To: Valerie Cross Dorn <vlc1@cornell.edu>

Cc: Francis Barany <barany@med.cornell.edu>, George Barany <barany@umn.edu>, Robert Hammer <rphammer@gmail.com>, lubingenetics@me.com <lubingenetics@me.com>, Maria Kempe <maria.kempe@med.lu.se>, Jim Kahn <jkahn@med.cornell.edu>, Brian Kelly <bjk44@cornell.edu>, Matt Pearson <mpearson@akingump.com>

Date Apr 21, 2017 at 1:48 PM

A headline that may be relevant to Illumina in the future.

https://twitter.com/johncarreyrou/status/855475560314785793

Sent from my iPhone

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Best,

Francis

[redacted]
barany@med.cornell.edu

[redacted]

———————

Dear Brian,

I appreciate all of the hard work by you and the team on this, and will be interested in learning more at the conference call. Please let me know what number to call in to.

Best wishes,

GB
--
George Barany
Distinguished McKnight University Professor of Chemistry
University of Minnesota
Department of Chemistry
[redacted]

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Francis, in addition to yourself, I have only received responses from Matthew Lubin and Bob Hammer that they will participate so I will circulate a dial-in number to those participants later today. I do not believe Mike Goldman or Carl Nathan were to be included in this call and I ask that you not include them on communications related to this call.

Thank you, Valerie

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Sorry, we have not received details for the call in.

In the interest of clarity and mindful of everyone's time, I am repasting below the questions that were important to the inventors (deleting those that are now no longer timely), as well as some new questions about the "without prejudice vs. with prejudice." clause.

Inventors: Would you please review questions to make sure those that are important to you are still included?

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Apr 19, 2017 | staff reporter

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Begin forwarded message:

From: GenomeWeb <newsletters@genomeweb.com>
Subject: Daily News: Illumina, Cornell Dismiss Patent Dispute
Date: April 19, 2017 at 4:01:51 PM EDT
To: <barany@med.cornell.edu>
Reply-To: <newsletters@genomeweb.com>

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Daily News

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Breaking News

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MeMed Awarded $9.2M DoD Contract

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Synpromics Raises £5.2M

The company intends to use a portion of the funding to further develop its PromPT synthetic promoter design platform. Read more >

ThermaGenix Completes $1.5M Series A-1 Financing

The funds will be used in part to support commercial activities related to the firm's ThermaStop and ThermaGo PCR additive reagents. Read more >

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Incorporating splicing and other clues from muscle transcripts, researchers reached diagnoses in cases that were inconclusive after sequencing alone. Read more >

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Presenters highlighted early work that supports the push for a national, systematic effort to elucidate progression from precancerous states to clinical malignancy. Read more >

SkylineDx Develops Tool to Predict Cancer Therapies Based on Genomic Data

The new algorithm, called TOPSPIN, complements the company's MMprofiler test. It is considering making TOPSPIN-generated data available to its MMprofiler patients. Read more >

Qiagen GeneReader Users Present Early Results at AMP Global Congress

Groups from Austria, Spain, Germany, and the US demonstrated that the GeneReader can reliably detect cancer mutations in tissue and liquid biopsy samples. Read more >

DNAlytics, VIB Partner to Develop Colorectal Cancer Screening Test

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One paper involving experts from Myriad Genetics and another from Invitae added fresh data to a contentious debate over the use of public variant databases.

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Director of Research and Development

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--
George Barany
Distinguished McKnight University Professor of Chemistry
University of Minnesota
Department of Chemistry
[redacted]

View less

Subject 0

From Monib Zirvi <matzirvi@yahoo.com>

To: Valerie Cross Dorn
<vlc1@cornell.edu>,
<rphammer@gmail.com>,
<lubingenetics@me.com>,
<mpearson@akingump.com>,
<maria.kempe@med.lu.se>,
<jkahn@med.cornell.edu>,
<michael.goldman@leclairryan.com>,
<barany@umn.edu>,
<barany@med.cornell.edu>,
<cnathan@med.cornell.edu>,
<bjk44@cornell.edu>

Date Apr 21, 2017 at 7:52 PM

Sent from my iPhone

0.pdf

The Facebook, Inc. v. Connectu, LLC et al Doc. 81

G. HOPKINS GUY, III (State Bar No. 124811)
hopguy@orrick.com
I. NEEL CHATTERJEE (State Bar No. 173985)
nchatterjee@orrick.com
MONTE COOPER (State Bar No. 196746)
mcooper@orrick.com
THERESA A. SUTTON (State Bar No. 211857)
tsutton@orrick.com
YVONNE P. GREER (State Bar No. 214072)
ygreer@orrick.com
ORRICK, HERRINGTON & SUTCLIFFE LLP
1000 Marsh Road
Menlo Park, CA 94025
Telephone: 650-614-7400
Facsimile: 650-614-7401

Attorneys for Plaintiffs
FACEBOOK, INC. and MARK ZUCKERBERG

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

SAN JOSE DIVISION

FACEBOOK, INC. and MARK ZUCKERBERG, Plaintiffs, v. CONNECTU, INC. (formerly known as CONNECTU, LLC), CAMERON WINKLEVOSS, TYLER WINKLEVOSS, DIVYA NARENDRA, PACIFIC NORTHWEST SOFTWARE, INC., WINSTON WILLIAMS, WAYNE CHANG, and DAVID GUCWA, Defendants.	Case No. 5:07-CV-01389-RS **DECLARATION OF THERESA A. SUTTON IN SUPPORT OF PLAINTIFFS' OPPOSITION TO CONNECTU'S CIVIL L.R. 6-3 MOTION TO ENLARGE TIME**

Dockets.Justia.com

I, Theresa Sutton, declare:

1. I am an attorney with the law firm of Orrick, Herrington & Sutcliffe LLP, counsel for Plaintiff Facebook, Inc. in the above captioned case. I am an active member in good standing of the California State Bar, and I am admitted to appear before this Court. I make this declaration based upon my own personal knowledge and knowledge of the documents in this case. If called as a witness, I could and would competently testify to the facts stated herein. The bases for Plaintiffs' Opposition to ConnectU's Civil L.R. 6-3 Motion to Enlarge Time are as follows:

2. ConnectU's motion purports to be brought pursuant to Civil Local Rule 6-3, which permits modifications of existing deadlines, but does not meet any of the explicit requirements of that Rule. ConnectU's motion contains requests for relief and argument that are not authorized by Rule 6-3. For instance, ConnectU asks the Court to

a. strike the Second Amended Complaint or order Facebook to withdraw it.

b. continue the July 11, 2007, Case Management Conference; and

c. prohibit Facebook from ever adding new parties to this action.

ConnectU also argues that the Second Amended Complaint violates this Court's May 21, 2007, Order granting Facebook leave to amend its Complaint.

3. ConnectU did not satisfy the requirements of Civil Local Rule 6-3. Rule 6-3 requires ConnectU to submit a declaration that: 1) sets forth with particularity, the reasons for the requested enlargement of time; 2) describes the efforts ConnectU has made to obtain a stipulation to the time change; 3) identifies the substantial harm or prejudice that would occur if the Court did not change the time; 4) discloses all previous time modifications in the case; and 5) describes the effect the requested time modification would have on the schedule for the case. The Declaration of Scott Mosko submitted in support of ConnectU's Motion to Enlarge Time does not include any of these factual statements.

4. ConnectU's Motion to Enlarge Time identifies no cognizable harm or prejudice that would occur if the Court denies its motion.

5. ConnectU's motion and, more specifically, the declaration submitted in support thereof, fails to describe the efforts ConnectU made to obtain a stipulation to the time change it now seeks.

6. Facebook did not violate the Court's May 21, 2007, Order granting Facebook leave to amend its complaint. The Order is silent on the issue.

7. Plaintiffs granted all defendants an extension of time to respond until June 25, 2007.

I declare under penalty of perjury that the foregoing is true and correct. Executed this 8th day of June, 2007, at Menlo Park, California.

/s/ Theresa A. Sutton /s/
Theresa A. Sutton

CERTIFICATE OF SERVICE

I hereby certify that this document(s) filed through the ECF system will be sent electronically to the registered participants as identified on the Notice of Electronic Filing (NEF) and paper copies will be sent to those indicated as non registered participants on June 8, 2007.

Dated: June 8, 2007.

Respectfully submitted,

/s/ Theresa A. Sutton /s/
Theresa A. Sutton

Subject The Facebook, Inc. v. Connectu, LLC et al :: Justia Dockets & Filings

From Monib Zirvi <matzirvi@yahoo.com>

To: Valerie Cross Dorn <vlc1@cornell.edu>, <rphammer@gmail.com>, <lubingenetics@me.com>, <mpearson@akingump.com>, <maria.kempe@med.lu.se>, <jkahn@med.cornell.edu>, <michael.goldman@leclairryan.com>, <barany@umn.edu>, <barany@med.cornell.edu>, <cnathan@med.cornell.edu>, <bjk44@cornell.edu>

Date Apr 21, 2017 at 7:54 PM

This is the approach we need to follow for Justice...

https://dockets.justia.com/docket/california/candce/5:2007cv01389/189975

Sent from my iPhone

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Date Apr 21, 2017 at 8:00 PM

This is the approach we need to follow for Justice...

http://www.businessinsider.com/how-mark-zuckerberg-hacked-connectu-2010-3

Sent from my iPhone

Subject How Facebook Was Founded

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<vlc1@cornell.edu>,
<rphammer@gmail.com>,
<lubingenetics@me.com>,
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<cnathan@med.cornell.edu>,
<bjk44@cornell.edu>

Date Apr 21, 2017 at 8:02 PM

http://www.businessinsider.com/how-facebook-was-founded-2010-3

Sent from my iPhone

Subject Re: CONFIDENTIAL: Dial-in Information for Conference Call re Settlement of Litigation

From George Barany <barany@umn.edu>

To: Valerie Cross Dorn <vlc1@cornell.edu>

Cc: Francis Barany <barany@med.cornell.edu>, Robert Hammer <rphammer@gmail.com>, lubingenetics@me.com <lubingenetics@me.com>, Monib Zirvi <matzirvi@yahoo.com>, Maria Kempe <maria.kempe@med.lu.se>, Jim Kahn <jkahn@med.cornell.edu>, Brian Kelly <bjk44@cornell.edu>, Matt Pearson <mpearson@akingump.com>

Date Apr 21, 2017 at 11:27 PM

Dear All,

I just want to thank each of you, attorneys and inventors alike, who participated in today's long and difficult conversation. Your thoughtfulness, candor, patience, and dedication are all very much appreciated. I do hope that we can develop a plan moving forward that reflects, in the best way possible, on our intellectual property and how it is perceived in the various communities that each of us operates in.

Best wishes,

GB

On Fri, Apr 21, 2017 at 10:00 AM, Valerie Cross Dorn <vlc1@cornell.edu> wrote:

> Here is the teleconference information for today's call at 2:30 Eastern Time (international dial-in included) to discuss settlement of the case against Illumina:
>
> **Dial-in Number (U.S. & Canada)**
> [redacted]
>
> **International Dial-in Number**
> [redacted]
>
> **Conference Code**
> [redacted]
>
> **Security Passcode**
> [redacted]
>
> We will confirm all participants at the start of the call, and reiterate the terms under which this call will take place. We will decline any discussion of steps going forward as that topic is beyond the agenda agreed upon for this call. Thank you,
>
> Valerie Cross Dorn
> Associate University Counsel
> Cornell University
> [redacted]
>
> On Apr 20, 2017, at 7:49 PM, Francis Barany <barany@med.cornell.edu> wrote:

Dear Valerie,

I agree with George, please send out the call information.

Please invite Matthew and all the inventors.

Thanks, and looking forward to the discussion tomorrow.

Best,

Francis

Sent from my iPhone

On Apr 20, 2017, at 6:54 PM, George Barany <barany@umn.edu> wrote:

> Dear All,
>
> Writing just for myself, I believe it would be very useful to proceed at the suggested time tomorrow, under the terms outlined by Valerie Cross Dorn (and conveyed in Brian Kelly's Friday e-mail). I commit to keeping confidential anything that is learned, particularly to the extent that information may be forthcoming that differs from what has been reported publicly. Several of us have already made appropriate arrangements with our schedules.
>
> I also appreciate Valerie's invitation (if I'm reading the e-mail correctly) for further dialogue that does not involve Matthew Pearson, and that may (or may not) involve Carl Nathan and/or Mike Goldman. I trust Francis and Valerie to work together on such an agenda, but in the meantime, let's move forward with tomorrow's call.
>
> Best wishes,
>
> GB
>
> On Thu, Apr 20, 2017 at 5:37 PM, Valerie Cross Dorn <vlc1@cornell.edu> wrote:
>
> > Francis, I have already explained to you and the other inventors why this call on Friday is being restricted to the inventors who were represented by Akin Gump during their participation in document collection and depositions for the case, based on the inventors' specific request to speak with Matthew.
> >
> > I asked for a commitment from those who are interested in participating in the discussion that was requested, under the confidential legend the invitation contained. You noted in an email yesterday at 11:45 a.m. that email is not the best form of communication and respectfully suggested that everyone participate in the call on Friday to hear the information we are able to share. Yet emails continue to circulate among you, making assertions without information other than what you have read in news reports, and those who declined the confidentiality request have not altered their positions, at least not as far as I can discern in the multiple emails sent since last Friday night. Please understand that there is no "full transparency" that applies when an attorney-client privilege applies.
> >
> > I am again requesting that you decide how you wish to proceed. Either notify us that you wish to go forward with the call under the confidentiality legend, and each of you commit to keep in

confidentiality legend, and each of you commit to keep in confidence the information we share that is not public, or we will need to remove Matthew Pearson from the call and you can proceed to discuss issues amongst yourselves.

Neither Carl Nathan nor Mike Goldman has a role in the discussion that was requested or arranged for this call. Therefore I do not anticipate they will be joining the call. However, if you wish to change the agenda, be clear that is what you are asking to do and we can respond accordingly. Absent clarification of what is to be discussed and the terms under which it will be discussed, it is difficult to arrange for this call to go forward.

I do have a conference line arranged and will forward it upon your clarification, under the guidance outlined in this email, and omit Mike Goldman and Carl Nathan. Thank you,

Valerie Cross Dorn
Associate University Counsel
Cornell University
[redacted]

On Apr 20, 2017, at 9:52 AM, Francis Barany <barany@med.cornell.edu> wrote:

Dear Valerie,

I do believe that George had sent an earlier email indicating his interest in the conference call. You may not have been copied on this correspondence, so I am re-pasting it into the email below.

Valerie, I politely suggest that the dial-in number be circulated to all the inventors, and they can decide on their availability to participate. Some of the material in the email below are relevant to those copied on this email — so in the interest of full transparency, they were included, but I do understand if you want to limit this particular call to just Cornell legal team, Matthew, and the inventors.

As mentioned below, the inventors have also requested that I represent them in a discussion about Cornell's next steps forward (which we believe should include both Carl Nathan and Mike Goldman).

Thank you for your good-faith willingness to help explain Cornell's perspective and rational for making these difficult decisions.

Best,

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[redacted]
barany@med.cornell.edu

[redacted]

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Begin forwarded message:

From: GenomeWeb <newsletters@genomeweb.com>
Subject: Daily News: Illumina, Cornell Dismiss Patent Dispute
Date: April 19, 2017 at 4:01:51 PM EDT
To: <barany@med.cornell.edu>
Reply-To: <newsletters@genomeweb.com>

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Synthetic Modification of Silica Beads That Allows for Sequential Attachment of Two Different Oligonucleotides

Gali Steinberg-Tatman, Michael Huynh, David Barker, and Chanfeng Zhao*

Illumina Inc., 9885 Towne Centre Drive, San Diego, California 92121. Received January 19, 2006; Revised Manuscript Received February 22, 2006

We developed a simple and elegant synthesis strategy that enables us to attach controlled (equimolar) amounts of two different oligonucleotides onto one silica bead. The method involves addition of orthogonally protected lysine followed by activation and derivatization of each amino group with a different moiety. This sequential oligonucleotide attachment enables the use of a combinatorial scheme to generate millions of bead types, each characterized by its two oligo tags. (In our randomly assembled arrays each bead type can then be identified by a series of hybridizations of fluorescently labeled decoder oligos to the address tags.) To demonstrate feasibility of such a scheme we created over 1000 bead types, which were characterized by their two oligo tags. The method enables genotyping or gene expression assays at multiplex levels of hundreds of thousands to millions.

INTRODUCTION

DNA array technology uses microscopic arrays of DNA molecules immobilized on solid supports for biomedical analysis of gene expression, polymorphism or mutation detection, DNA sequencing and gene discovery (*1*, *2*).

Conventional microarrays are manufactured by spotting or synthesizing probes at known locations on a two-dimensional substrate (*3*−*5*).

Illumina's novel approach (*6*) enables the production of randomly assembled arrays in which the location of a probe is initially unknown (*7*). Random bead loading combined with decoding, described in detail previously (*6*), avoids the need for physical addressing of each element and thus achieves very high packing densities by using relatively simple bulk processes. The decoding process is efficient and extremely accurate (*6*). However, it requires at least one fluorescently labeled decoder oligo for each unique bead type. For very large numbers of bead types (tens to hundreds of thousands), a more practical decoding approach uses two different address oligos on each bead. This reduces the number of decoder oligos required to two times the square root of the number of unique beads. For example, to decode 1 million different bead types would require only 2000 oligo decoders. Figure 1 illustrates three potential schemes for attaching two different oligonucleotides to the same bead. In this paper, we focus on methods for groups A and B.

To enable sequential attachment of two distinct moieties to one bead, we developed an alternative chemistry scheme involving the use of orthogonally protected lysine. The two amino groups on the lysine are sequentially activated, permitting sequential addition of two different oligonucleotides. The approach is general and could be used to attach different chemical moieties to the same bead, such as an oligo and a peptide.

EXPERIMENTAL PROCEDURES

Chemical Reagents. Silica beads in water (3 μm diameter, $\sim 5 \times 10^{10}$ beads/g) were obtained from Bangs Laboratories Inc., Carmel, IN. Silanization reagent, 3-aminopropyltrimethoxysilane, was obtained from United Chemical Technologies (UCT), Bristol, PA. Succinimidyl 4-formylbenzoate (SFB) and succinimidyl hydraziniumnicotinate hydrochloride (SHNH) were obtained from Solulink, San Diego, CA. Oligonucleotides were obtained from Operon Technologies, Alameda, CA, or synthesized in house. All oligonucleotides obtained from Operon Technologies were HPLC purified. Other reagents were obtained from NovaBiochem, Aldrich, or Sigma. All solutions were prepared with OmniPur (sterile, nuclease free) water from Merck.

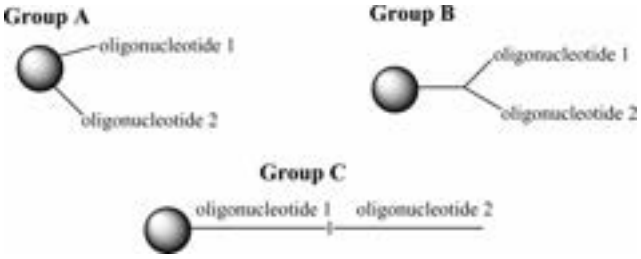

Figure 1. Potential schemes for two oligonucleotide attachment.

Surface Modifications. *Silanization.* Silica beads (1 g) were washed with 10 mL ethanol (HPLC grade). The beads were then suspended in 10 mL of ethanol followed by addition of 50 μL (0.5%) silane reagent, and shaken for 1 h at room temperature. Following silanization they were washed 5 times with 10 mL of ethanol and 3 times with 10 mL of ether, dried, and stored at room temperature. (Silanization is shown in Figure 2.)

Ninhydrin Test. Completion of various reaction steps was monitored (qualitatively) using the ninhydrin test as follows: A small amount of ninhydrin solution (10 wt % ninhydrin in ethanol) was heated to 120 °C, a smidgen of beads was added to one test tube, and another was used as reference. When primary amines were present on the beads, ninhydrin solution turned blue; otherwise, the color of the solution remained unchanged.

Chemical Modifications of Silanized Beads. Figure 2 shows the synthetic approach to sequential oligonucleotide attachment, as demonstrated in the potential scheme in Figure 1 group A.

Coupling of Fmoc and t-Boc Protected Glycines to Silanized Beads. Aminopropyl beads (100 mg) were suspended in DMF

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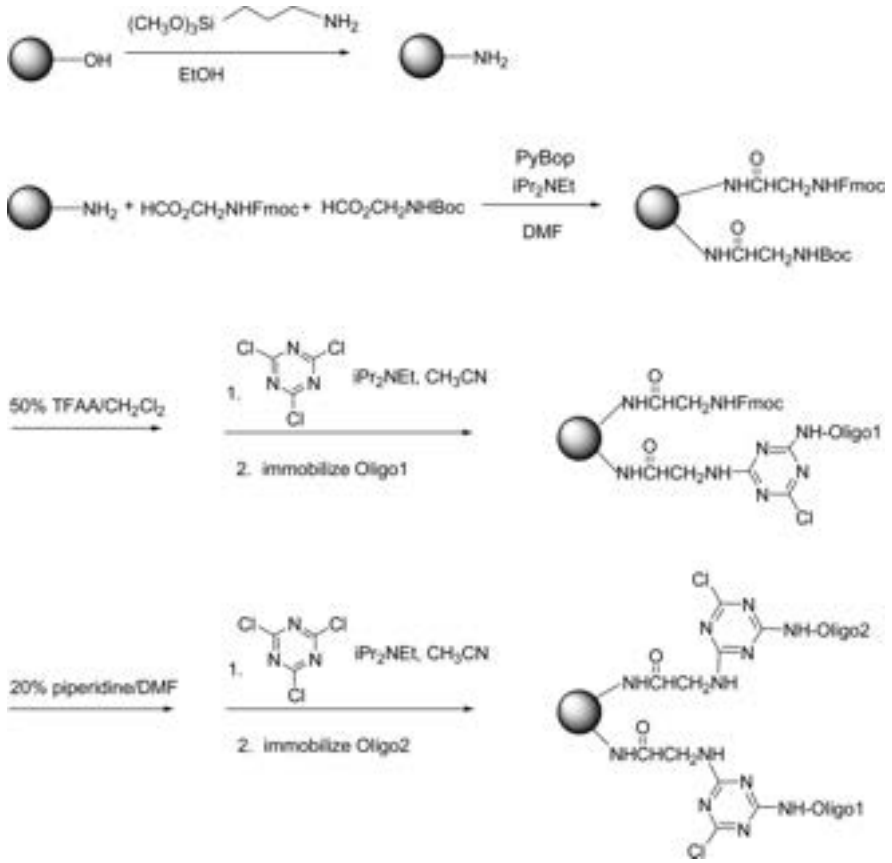


Figure 2. Detailed chemical modifications of hydroxyl beads leading to two oligonucleotide attachment, as depicted in Figure 1, group A.

(1 mL), followed by addition of 35 μL of *N*,*N*-diisopropylethylamine (DIEA) (0.2 mmol). The suspension was sonicated, and an equimolar (1:1) mixture of *N*-α-*t*-Boc-glycine (8.75 mg, 0.05 mmol) and *N*-α-Fmoc-glycine (14.85 mg, 0.05 mmol) was added. This was followed by the addition of 52 mg (0.1 mmol) of PyBOP (benzotriazole-1-yl-oxy-tris-pyrrolidinophosphoniumhexa fluoro phosphate). The beads were shaken overnight at room temperature. They were then washed 6 times with 1 mL of DMF and 3 times with methylene chloride.

Amine Deprotection (from t-Boc). Beads coupled to the modified lysine (100 mg) were suspended in a solution of 50% trifluoroacetic acid in methylene chloride (1 mL) and shaken for 30 min at room temperature. They were then washed 3 times with 1 mL of methylene chloride and 3 times with 1 mL of acetonitrile.

Cyanuric Chloride Activation. Amino beads (100 mg) were suspended in acetonitrile (1 mL), followed by addition of 20 μL (0.12 mmol) of DIEA. After a brief sonication, 10 mg (0.05 mmol) of cyanuric chloride was added and the reaction mixture was shaken for 2 h at room temperature. The beads were washed 3 times with 1 mL of acetonitrile and twice with 1 mL of 0.05 M sodium borate buffer (pH 8.5).

Amine Deprotection (from Fmoc). Beads coupled to the modified lysine (100 mg) were suspended in a solution of 20% piperidine in DMF (1 mL) and shaken for 30 min at room temperature. They were then washed 3 times with 1 mL of DMF and 3 times with 1 mL of acetonitrile.

Figure 3 shows the potential schemes of group B from Figure 1. Both address and assay oligonucleotide sequences that can be attached to beads in these schemes.

Figure 4 shows the synthetic approach to sequential oligonucleotide attachment, as demonstrated in the potential scheme in Figure 1 group B.

Coupling of Orthogonally Protected Lysine to Silanized Beads. Aminopropyl beads (100 mg) were suspended in DMF

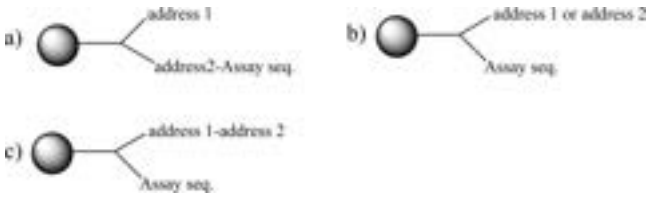


Figure 3. Detailed potential encoding schemes of group B from Figure 1.

(1 mL), followed by addition of 35 μL of DIEA (0.2 mmol). The suspension was sonicated and *N*-α-Fmoc-*N*-ε-1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)-3-methylbutyl-L-lysine (53 mg,0.1 mmol) was added followed by addition of 52 mg (0.1 mmol) of PyBOP (benzotriazole-1-yl-oxy-tris-pyrrolidinophosphoniumhexa fluoro phosphate). The beads were shaken overnight at room temperature. They were then washed 6 times with 1 mL of DMF.

Amine Deprotection (from Dde(iv), (4,4-Dimethyl-2,6-dioxocyclohexylidene)-3-methylbutyl). Beads coupled to the modified lysine (100 mg) were suspended in a solution of 2% hydrazine in DMF (1 mL) and shaken for 30 min at room temperature. They were then washed 6 times with 1 mL of DMF.

Figure 5 shows alternative approaches to the activation of the second amino group and immobilization of second oligonucleotide.

Coupling to Succinimidyl Hydraziniumnicotinate Hydrochloride (SHNH). Amino beads (100 mg) were suspended in DMF (1 mL), followed by addition of SHNH (28.6 mg, 1 mmol) and 48 μL of DMAP solution (dimethyl amino pyridine in DMF 0.5 M). The beads were shaken overnight at room temperature and then washed 3 times with DMF and 3 times with 0.1 M sodium citrate buffer, pH 5.0.

Coupling of amino beads to PDITC (1,4-phenylene diisothiocyanate), 4-nitrophenyl chloroformate, 4-carboxybenzaldehyde,

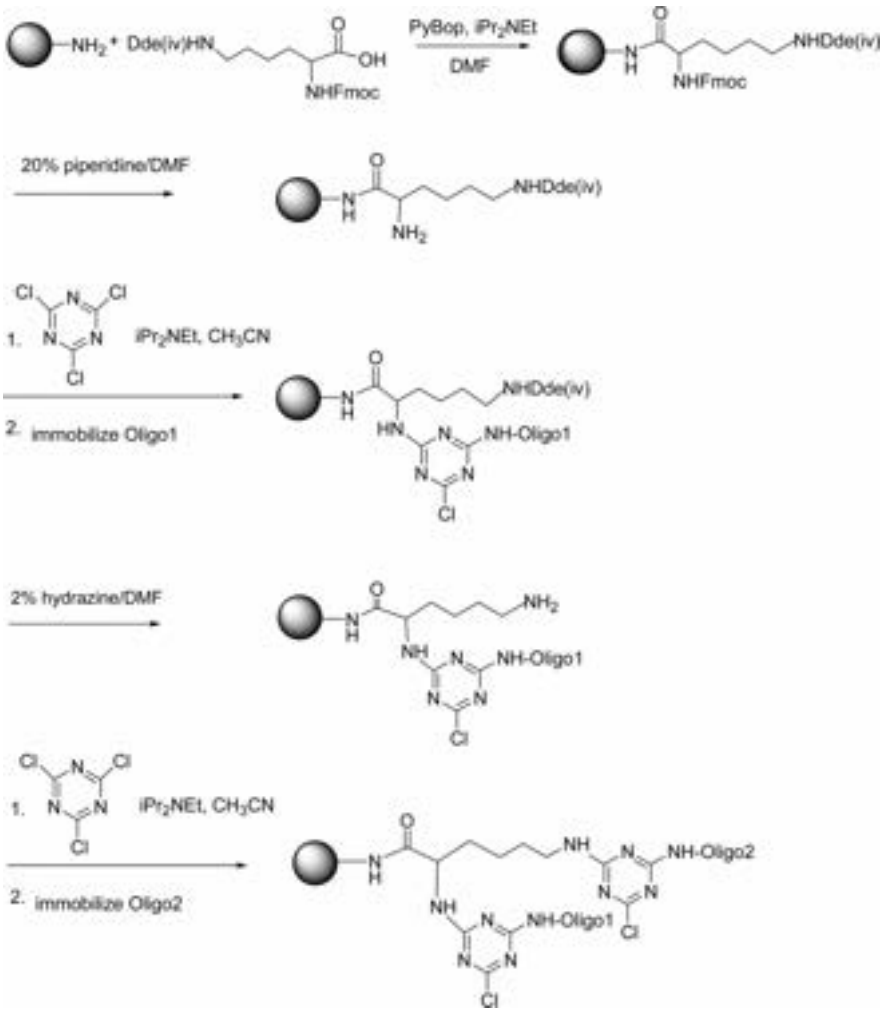


Figure 4. Detailed chemical modifications of amino silanized beads leading to two oligonucleotide attachment, as depicted in Figure 1, group B.

and succinimidyl 4-formylbenzoate (SFB) has been previously described (*8*), see Figure 5A−D.

Oligo Immobilization. *Amino Oligonucleotide Immobilization.* A 5′-amino oligonucleotide (100 nmol in 0.05 M sodium borate buffer, pH 8.5) was added to 2 M sodium chloride solution (100 μL). The oligonucleotide solution was added to cyanuric chloride activated beads (25 mg beads in 100 μL of 0.05 M sodium borate buffer, pH 8.5). The beads were shaken overnight and then washed 3 times with OmniPur water.

5′-Amino oligonucleotides were synthesized in house using the standard coupling conditions and 5′-amino modifier phosphoramidite commercially available from Glen Research, Sterling, VA.

Aldehyde Oligonucleotide Immobilization. A 5′-aldehyde oligonucleotide (100 nmol in 0.1 M sodium citrate/citric acid, pH 5.0) was added to 2 M sodium chloride solution (100 μL). The oligonucleotide solution was added to hydrazine-activated beads (25 mg of beads in 100 μL of 0.1 M sodium citrate/citric acid, pH 5.0). The beads were shaken overnight and then washed 3 times with OmniPur water.

5′-Aldehyde oligonucleotides were synthesized in house using the standard coupling conditions and 5′-aldehyde phosphoramidite commercially available from Solulink, San Diego, CA.

Complementary Oligonucleotide (Target) Hybridization. Hybridization of complementary oligo (target) to beads containing immobilized probes was carried out in solution, and a fluorescence activated cell sorter (FACS) was used to measure hybridization intensity.

Hybridization was done in solution as follows. About 1 mg of probe-immobilized beads was suspended in 30 μL of hybe buffer (0.1 M potassium phosphate, 1 M sodium chloride, 0.1% Tween-20, and 5% ethanol, pH 7.6), followed by addition of 15−20 μL of ∼1 mM target (in 0.05 M borate buffer, pH 8.5) and then shaken for 2 h. The beads were washed 2 times with hybe buffer to remove excess target oligonucleotides. For the release of target from the beads, the beads were incubated with 50 μL of 0.1 M sodium hydroxide solution for 10 min.

Detection of Hybridization. Hybridization in solution was measured with FACS (Becton Dickinson Biosciences). We used constant laser power of 15 mW and a photomultiplier tube (PMT) gain of 659 for all measurements. Following hybridization in solution (described in the previous section), a small amount of beads was added to 0.2 mL of FACS flow buffer (in a FACS-compatible test tube), and average fluorescence intensity was recorded for at least 10 000 beads.

RESULTS AND DISCUSSION

Addressing Beads with Multiple Oligonucleotides. Various schemes, shown in Figure 1, were considered in an attempt to generate millions of bead types using a combinatorial approach. These schemes can be divided into 3 main groups: group A (where two orthogonally protected glycines are coupled to the beads followed by sequential oligonucleotide immobilization), group B (where one orthogonally protected lysine is coupled to the beads followed by sequential oligonucleotide immobilization), and group C (where one long oligonucleotide, which includes both address sequences, is immobilized).

The scalability of these schemes was evaluated based on the required number of oligonucleotides, the number of decoder

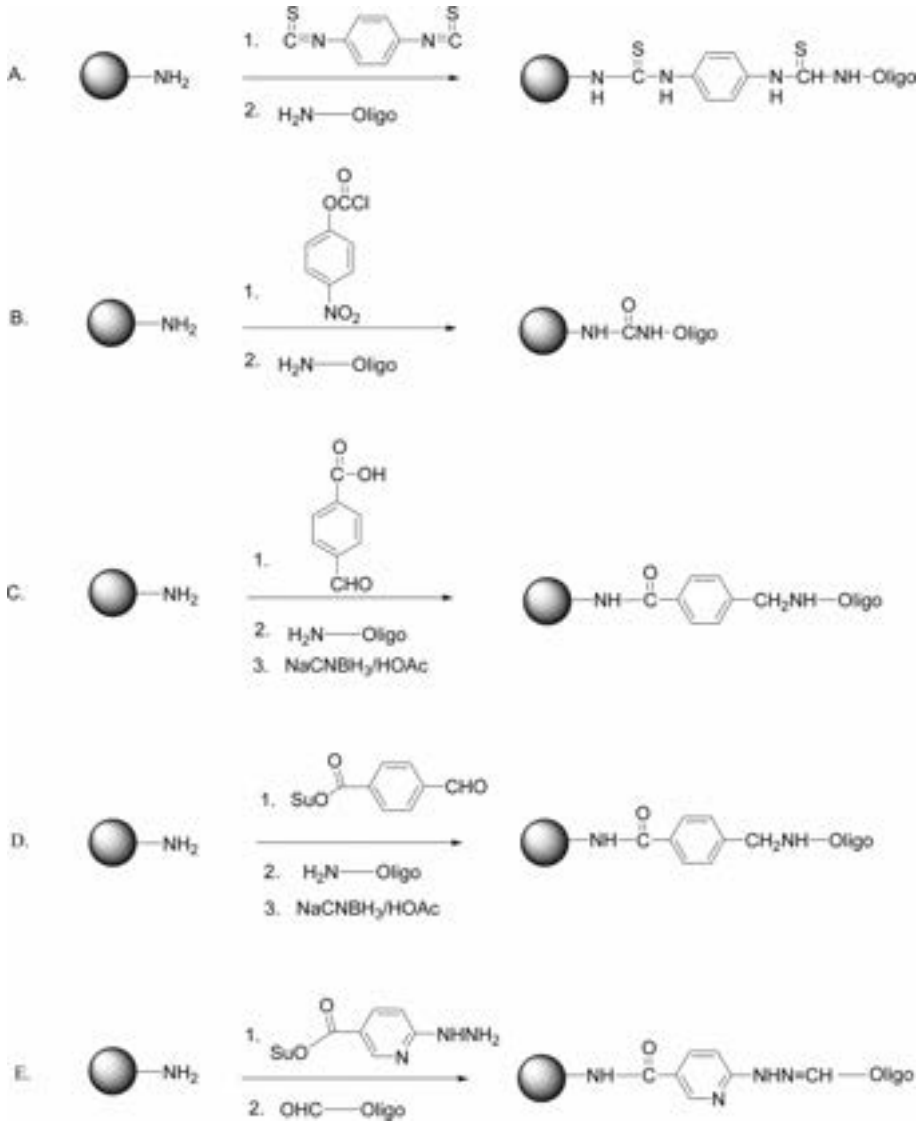


Figure 5. Alternative activation/immobilization schemes for second oligonucleotide attachment.

oligonucleotides, and the number of split and pool synthesis steps that would be necessary to implement a particular chemistry in an automated, high-throughput environment.

Group C schemes, while this study was carried out, involving one very long (100-mer) oligonucleotide, were not considered because low synthesis yields would be expected. Group A type schemes were evaluated first. The synthesis, shown in Figure 2, involved coupling of two orthogonally protected glycines to aminopropyl (silanized) beads as described in Experimental Procedures. The coupling was followed by deprotection of the *t*-Boc protected glycine and its activation with cyanuric chloride. The activation was followed by immobilization of an amino modified oligonucleo-tide. Following immobilization, the Fmoc protected glycine was deprotected with 20% piperidine solution, and the amine was activated with cyanuric chloride. Finally, another amino modified oligonucleotide (containing assay specific sequence) was immobilized as well.

Group A schemes, however, have an inherent problem. Since two orthogonally protected glycines are coupled to the beads simultaneously, it is hard to control the amount of each glycine that will couple to the amino beads. As a result, it is difficult to control the ratio of immobilized oligonucleotides, which can impact the decoding and/or assay robustness. In schemes from group B the aforementioned problem is avoided as only one orthogonally protected amino acid is coupled to the amino beads. The potential schemes for group B are shown in Figure 3.

The synthesis of group B schemes, shown in Figure 4, involved coupling of a lysine, with two orthogonally protected amino groups, to aminopropyl (silanized) beads as described in Experimental Procedures. The coupling was followed by the deprotection of the Fmoc protected amino group and its activation with cyanuric chloride. Immobilization of a single amino modified address oligonucleotide or an equimolar mix of two amino modified address oligonucleotides followed the activation. Then the second protecting group (Dde(iv)) was removed with 2% hydrazine in DMF solution and the second amine was again activated with cyanuric chloride. Finally amino modified oligonucleotide (containing assay specific sequence) was immobilized (as described in Experimental Procedures).

Variation in Signal Intensities of Oligonucleotides. After the first amino group was activated with cyanuric chloride (see Figure 4), an equimolar mix of oligonucleotide 1 and oligonucleotide 2 was immobilized onto the bead (Figure 3b). In spite of using only HPLC purified oligos, hybridization intensities for the various oligonucleotides varied sometimes by more than 10-fold. Even for the same oligonucleotides, signal intensity varied up to 2−3-fold depending on the neighboring sequence (i.e. the other oligonucleotide that was immobilized with it).

Although not as pronounced, these variations in hybridization signals were observed even on beads with a single oligonucleotide immobilized on them. To understand the reasons behind the variation in hybridization signals we first looked at beads

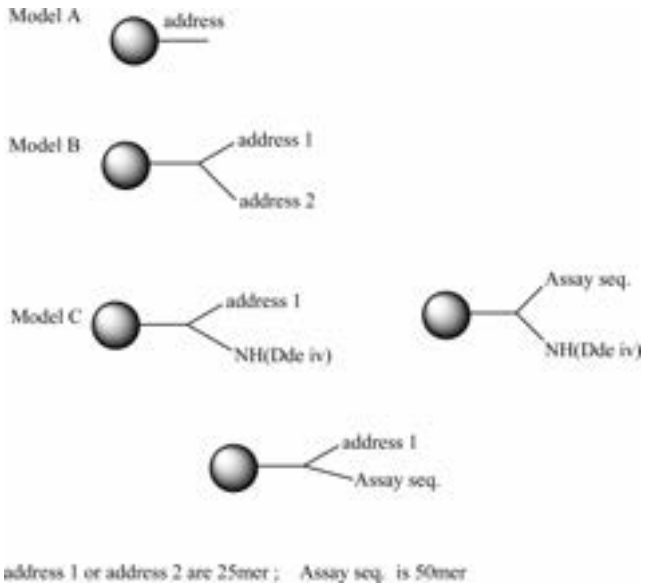
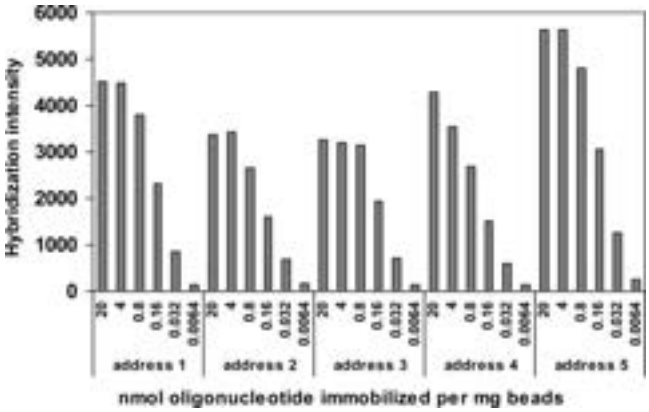


Figure 6. Bead models used for proof of various principles.

Chart 1. Effect of Titration of Oligonucleotide Amount on Beads for 5 Random Address Sequences (25mers)



immobilized with only a single type of oligonucleotide (Figure 6, model A). Since we use excess oligo during the immobilization process (4 nmol of oligo per 1 mg of beads), we believe that the amount of oligo immobilized is consistent regardless of the sequence involved. To demonstrate the fact that a consistent amount of oligonucleotide is immobilized, the beads were immobilized at six different oligonucleotide concentrations ranging from 20 to 0.0064 nmol per mg of beads. These titration results for five address sequences are shown in Chart 1.

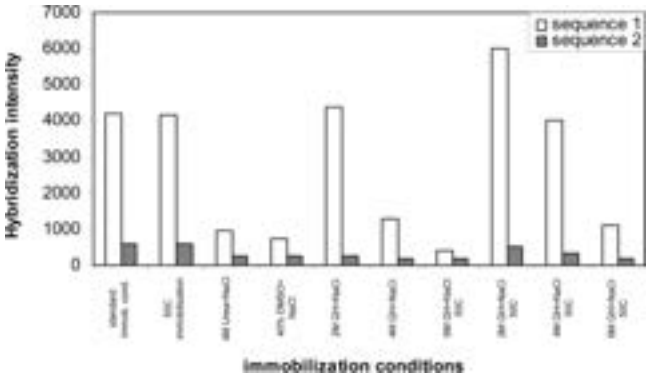
Another possible reason for variation in hybridization intensities could be variation in hybridization efficiency. This can be a result of sequence dependence or a result of variation in material quality.

To address variation in material quality, several oligonucleotides from different synthesis batches were immobilized on beads (single oligonucleotide immobilization) and then hybridized to the same target labeled oligos. The intensity of hybridization signals was measured using FACS.

Results show that there is similarity between hybridization intensities of the same sequences from different synthesis batches. This observation suggests that the major contribution to the variation in hybridization intensities comes from sequence variation, although material quality also contributes somewhat.

When two oligonucleotides are immobilized simultaneously (as in Figure 3b), the picture becomes even more complex, since oligonucleotide interactions can now come into play. Since immobilization kinetics can be different for different sequences,

Chart 2. Effect of Various Immobilization Conditions (Known To Disrupt Secondary Structure) on Hybridization Intensities of Two Oligonucleotides Immobilized Simultaneously[a]



[a] Standard immobilization conditions (described in detail in Experimental Procedures) include 2 M NaCl and room temperature (a). To disrupt secondary structure immobilization was done at 50 °C (b), urea was added to a final concentration of 4 M (c), dimethyl sulfoxide (DMSO) was added to a final concentration of 40% (d), guanidinium hydrochloride (GH) was added to a final concentration of 2 M (e), 4 M (f), and 6 M (g). Also guanidinium hydrochloride was added to a final concentration of 2 M (h), 4 M (i), or 6 M (j) and immobilization was done at 50 °C.

we could have unequal amounts of the two oligonucleotides immobilized on the beads, which could result in very different hybridization intensities. To test whether the source of variation in the hybridization signals of oligonucleotides (immobilized simultaneously) is a result of unequal amounts of oligonucleotides immobilized on the beads, we attempted to equalize their immobilization kinetics by disrupting their secondary structure.

The immobilization procedure was carried out both under the usual conditions (see Experimental Procedures) and under conditions which are known to disrupt secondary structures, such as high temperatures (50 °C) and high concentrations of either urea (4 M) or guanidinium hydrochloride (6 M).

Chart 2 shows that, despite disruption of secondary structure, sequence 1 continues to yield much higher hybridization intensities than sequence 2. These observations suggest that, since equal amounts of the two oligonucleotides are immobilized, the variation in hybridization signals is a result of differences in hybridization efficiency for different sequences. It is still unclear why the variation in hybridization signals becomes more pronounced when two oligonucleotides are immobilized simultaneously on the bead.

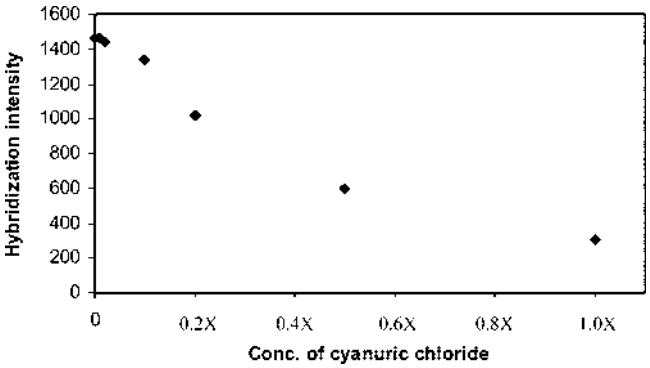
We concluded that, if the scheme in Figure 3b were chosen, all oligonucleotides would have to be prescreened prior to use to select pairs with similar hybridization signals after immobilization. Since this problem is mainly sequence related, the screening would have to be done only once. Another way to avoid the problem would be to use the scheme in Figure 3a or the scheme in Figure 3c where immobilizations of the different oligonucleotides are done sequentially.

Immobilization of Second Oligonucleotide (Genespecific Assay Sequence). After either one or two oligonucleotides were immobilized on the first amino group (Figure 3a−c), the second amino group was then activated prior to the immobilization of the second oligonucleotide. As shown in Figure 4, the amine was deprotected with 2% hydrazine/DMF solution and then activated with cyanuric chloride. Following activation, a severe drop in the hybridization intensity of the first oligonucleotide(s) was observed. Apparently, cyanuric chloride damages the oligonucleotides already present on the beads and leaves them unable to hybridize well.

Table 1. Hybridization Intensities of First and Second Sequences Resulting from the Different Activation/Attachment Chemistries for the Second Sequence

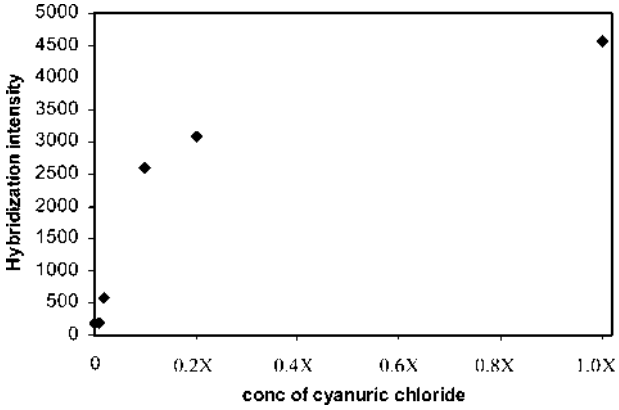
1st Sequence: S9 5′ (NH_2) TTTGATGTCCCATTCCCCACGCGTT					
2nd Sequence: S13 5′ (NH_2 or CHO) TTTGATCGTAGCCGGTATGCGACGG					
immobilization chemistries for 2nd attachment	5A	5B	5C	5D	5E
hybridization intensity of the 1st sequence before the 2nd sequence was immobilized	4978	5100	5154	5120	4978
hybridization intensity of 1st sequence after the 2nd sequence was immobilized	3925	2640	2729	2852	2670
hybridization intensity of the 2nd sequence	808	205	457	430	2950
1st Sequence: S13 5′ (NH_2) TTTGATCGTAGCCGGTATGCGACGG					
2nd Sequence: S9 5′ (NH_2 or CHO) TTTGATGTCCCATTCCCCACGCGTT					
immobilization chemistries for 2nd attachment	5A	5B	5C	5D	5E
hybridization intensity of the 1st sequence before the 2nd sequence was immobilized	3095	2872	2950	2930	3093
hybridization intensity of 1st sequence after the 2nd sequence was immobilized	2488	1500	1580	1550	1650
hybridization intensity of the 2nd sequence	1400	108	800	820	4800

Chart 3. Effect of Cyanuric Chloride Concentration on the Ability of Capture Probes To Hybridize Their Complement (Target)[a]



[a] During this experiment oligo-immobilized beads were shaken with cyanuric chloride for 2 h. 1X is the concentration normally used to activate our beads with cyanuric chloride, prior to oligonucleotide attachment.

Chart 4. Effect of Cyanuric Chloride Concentration (during Activation of Amino Beads) on Oligonucleotide Immobilization and Consequently Hybridization Intensities of These Oligonucleotides



The effect of cyanuric chloride concentration on the ability of capture probes to hybridize with their complement (target) was examined on a model bead (Figure 6, model A). The amount of cyanuric chloride that was added to oligo-immobilized beads was titrated as shown in Chart 3 (the beads were shaken with various amounts of cyanuric chloride for 2 h to emulate the conditions of an activation reaction).

Titration results show that, when the standard amount of cyanuric chloride (1X = 0.05 mmol) is shaken with oligonucleotide-immobilized beads for 2 h, up to a 5-fold drop in hybridization signal results (relative to beads that are not treated with cyanuric chloride). We then examined the effect of reducing cyanuric chloride concentration on the hybridization signal of oligonucleotides being immobilized. Chart 4 shows that reducing the amount of cyanuric chloride will decrease the hybridization signal of the oligonucleotide that is being immobilized.

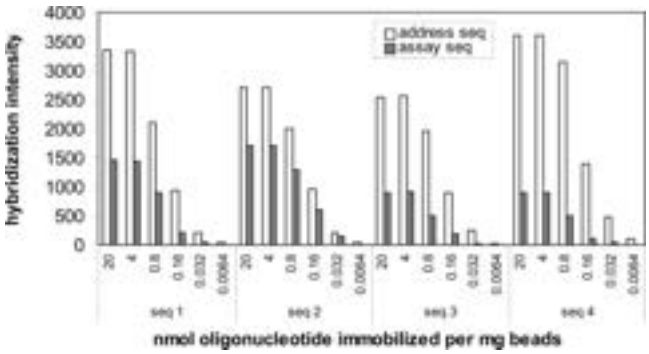
This model study suggests that, if we use our standard cyanuric chloride concentration for the activation of the second amine group, up to 80% loss in hybridization intensity may be observed for the first oligonucleotides attached. If the amount of cyanuric chloride is reduced for the activation of the second amine group, there will be loss of hybridization intensity for the second oligonucleotide immobilized. Several attempts to optimize the amount of cyanuric chloride to be used during second amine activation proved unsuccessful. To prevent the drop in hybridization intensities of the first address oligos, new activation schemes were considered for the second amine. In all cases we examined the effect of a particular activation reaction on the hybridization intensities of the first oligonucleotide as well as the second oligonucleotide.

Based on results from our previous paper (*8*), where various amino group activation (and oligonucleotide immobilization) schemes were tested, the reaction schemes shown in Figure 5 were considered.

Model beads with two address sequences (Figure 6, model B) were synthesized, with the second amine group activated (and second oligonucleotide immobilized) according to the five different schemes shown in Figure 5. Table 1 summarizes hybridization intensities for both the first and second address sequences, for all of the schemes in Figure 5. The most promising scheme seems to be that in Figure 5E, where the amine was coupled to an activated ester hydrazine and a hydrazone bond was formed with the aldehyde-modified oligonucleotide. We observed very little signal loss for the first oligonucleotide and very good intensities for the second oligonucleotide.

Optimization of Capture Probe Loading. In our previous paper (*8*) we first optimized oligo loading (using 5′ amino labeled and 3′ Fmoc labeled oligos) and then measured the hybridization efficiency for single attachment beads. After coupling the beads to the modified lysine (see Figure 4) we have a different number of amino sites available for activation/immobilization and at a different proximity. As a result it is important to optimize the amount of oligo that we need to immobilize on these double-attachment beads in order to obtain the highest possible hybridization signals. In these experiments maximal hybridization efficiencies or oligo loading was not investigated; instead, when choosing the optimal oligo concentration for immobilization, we were more interested in hybridization intensities (functional results). Titration of oligonucleotide concentration during immobilization was done for several model beads. The titration was accomplished for beads with address oligonucleotides (25mers), beads with assay sequences (50mers), and beads with both oligonucleotides immobilized together on the two attachment beads (see Figure 6, model C). Chart 5 shows that maximal hybridization intensities were observed in the same range of oligonucleotide concentration (1−4 nmol of oligonucleotide per 1 mg of beads) regardless of oligonucleotide length. Similarly, maximal hybridization intensi-

Chart 5. Effect of Titration of Oligonucleotide Amount on Two Attachment Beads Shown in Figure 6 Model C, for 4 Random Address Sequences (25mers) and 4 Random Assay Sequences (50mers)



ties were observed in the same range of oligonucleotide concentration when both oligonucleotides were immobilized on the bead (results not shown).

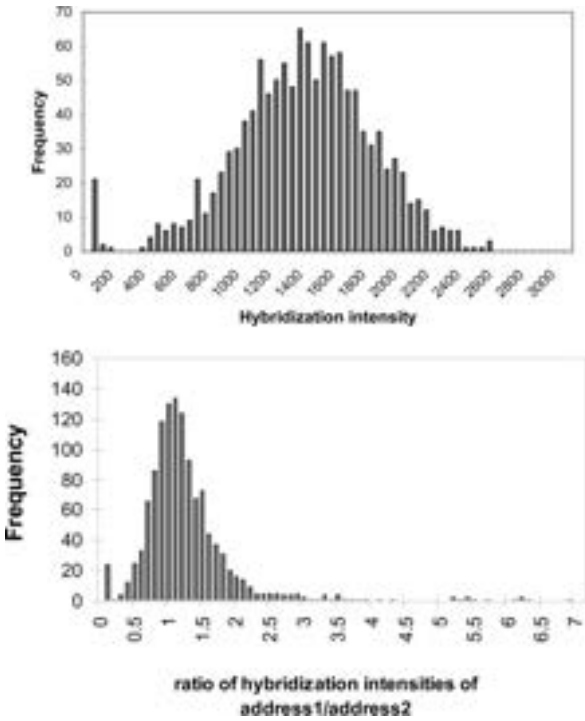
Scale-Up to Over 1000 Bead Types. In order to test the scalability of our schemes (Figure 3a,b, group B), we prepared over 1000 bead types (using each scheme). In each of these schemes two address oligos were used, allowing us to create over 1000 bead types with a mere 60−70 address oligonucleotides.

Since the number of address oligonucleotides required is two times the square root of the number of unique beads, to create 1225 bead types requires only 70 address sequences. These address sequences were chosen out of 1100 random address sequences following a quick screening process where 4−5 address sequences were immobilized on a bead simultaneously, and 70 sequences that give the highest as well as similar hybridization intensities were then chosen. The address sequences were divided into two groups (address sequence 1 and address sequence 2) of 35 oligonucleotides each. Initially synthesis steps described in Figure 4 were followed; then after the first amine activation the beads were distributed into thirteen 96 well plates and to each well an equimolar mix of address sequence 1 and address sequence 2 (all possible combinations) was added creating 1225 unique bead types (immobilization is described in Experimental Procedures). The immobilization was followed by deprotection of the second amine (see Figure 4). The beads were then hybridized to the complementary FAM labeled targets one at a time (either complement to address sequence 1 or to address sequence 2), and hybridization intensities were measured on FACS. Distribution of the hybridization intensities is shown in Chart 6.

Chart 6 shows that hybridization intensities for the various bead types range from 400 to 2400 counts, and the ratio of hybridization intensities of address sequence 1 to address sequence 2 is around one. These hybridization intensities appear to be sufficient for a robust decoding. The main drawback of this model is the prescreening that must be done for the address oligonucleotides due to the interactions that were observed between oligonucleotides (causing extreme variations in hybridization intensities) when two or more were immobilized simultaneously.

Similarly, the scale-up for the scheme in Figure 3a was done using 64 address sequences creating 1024 unique bead types. The scale-up for the scheme in Figure 3a was done using a model for the scheme to demonstrate feasibility of scale-up (see Figure 6, model B). The address sequences were divided into two groups (address sequence 1 and address sequence 2) of 32 oligonucleotides each. Initially synthesis steps described in Figure 4 were followed; then after the first amine activation the beads were distributed into a 96 well plate, and one of the

Chart 6. Distribution of Hybridization Intensities for 1225 Two Attachment Beads Hybridized to Complement of Address 1



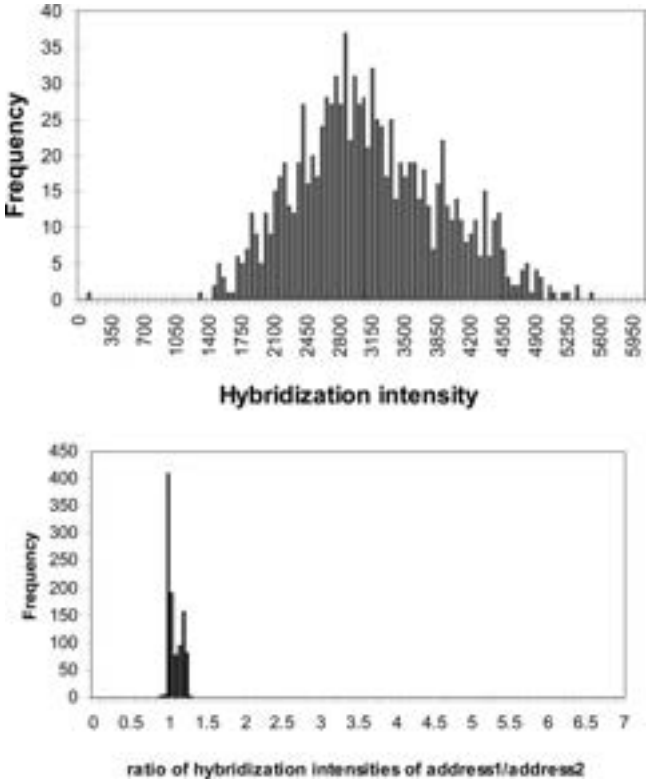
oligonucleotides from the first group (address sequence 1) was added to each well (immobilization is described in Experimental Procedures). The second amine was then deprotected and coupled to SHNH (see Figure 5 scheme E). Finally, beads from each well were distributed into 32 wells and immobilized with each of the 32 oligonucleotides from the second group (address sequence 2). The beads were then hybridized to the complementary FAM labeled targets one at a time (complement either to address sequence 1 or to address sequence 2), and hybridization intensities were measured on FACS. Distribution of the hybridization intensities is shown in Chart 7.

Chart 7 shows that hybridization intensities for the various bead types range from 1400 to 5000 counts, and the ratio of hybridization intensities of address sequence 1 to address sequence 2 is around one. The hybridization intensities are quite high and are more than sufficient for robust decoding. Even more importantly the address sequences were chosen completely at random yet hybridization intensities were fairly similar. We believe this is because the address sequences are immobilized separately and therefore there is no interaction between them during immobilization (see section about variation in signal intensities of oligonucleotides). One of our concerns was that there were reactive sites remaining after immobilization of oligo1; in such a case, oligo2 could immobilize on these reactive sites. However, the observation that the ratio of hybridization intensities of address sequence 1 to address sequence 2 is around one suggests that, if this type of immobilization is taking place, it is minimal; otherwise we would expect this ratio to be much less than one.

CONCLUSIONS

We evaluated several schemes for attaching two oligonucleotides on one bead. The schemes fall into 3 main groups. In the first group the oligonucleotides are sequentially immobilized following a simultaneous coupling (to the beads) of two orthogonally protected glycines. In the second group the oligonucleotides are sequentially immobilized following coupling of the beads to orthogonally protected lysine, and in the third group the oligonucleotides are synthesized in one long

Chart 7. Distribution of Hybridization Intensities for 1024 Two Attachment Beads Hybridized to Complement of Address 1



sequence and immobilized as one oligonucleotide. After schemes from group A and group C were rejected for various reasons (see Results and Discussion), we evaluated schemes from group B (shown in Figure 3). We found that, if two oligonucleotides are immobilized simultaneously (as in Figure 3b), they interact during immobilization and as a result their hybridization intensities can be vastly different. We also found that, in Figure 3a where the address sequences are immobilized sequentially, the differences in hybridization intensities are less pronounced, which allows us to avoid prescreening of the address sequences.

We also found that cyanuric chloride damages oligonucleotides and therefore activation of the second amine required a different chemistry. After testing five different approaches for amine activation and oligonucleotide immobilization, we showed that the best method involves amine coupling to an activated ester hydrazine and immobilization of an aldehyde-modified oligonucleotide.

Loading of oligonucleotides on beads was shown to be independent of oligonucleotide length and independent of whether one oligonucleotide or two (through lysine coupling) were immobilized.

Finally, in order to test the scalability of our schemes (Figure 3a,b) we prepared over 1000 bead types (using a model of each scheme). In each of these models two address oligos were used, allowing us to create over 1000 bead types with a mere 60−70 address oligonucleotides. We found that both approaches were successful. Hybridization intensities for all bead types were similar, and the ratio of hybridization intensities of address sequence 1 to address sequence 2 was around one. The hybridization intensities were quite high and were more than sufficient for robust decoding. The scheme in Figure 3a, however, has an advantage over the scheme in Figure 3b because the address sequences are immobilized separately and therefore there is no competition during immobilization so the address sequences can be chosen at random. In contrast, the scheme in Figure 3b requires prescreening of address sequences.

ACKNOWLEDGMENT

We would like to thank Dr. Semyon Kruglyak and Illumina's Bioinformatics group for all their help with image registration and analysis, and Dr. Igor Kozlov and the chemistry group for support and discussion.

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(2) Freeman, W. M., Robertson, D. J., and Vrana, K. E. (2000) Fundamentals of DNA Hybridization Arrays for Gene Expression Analysis. *BioTechniques 29*, 1042−1055.

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BC060012V

Subject Re: bc060012v

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To: Valerie Cross Dorn
<vlc1@cornell.edu>,
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<lubingenetics@me.com>,
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<jkahn@med.cornell.edu>,
<michael.goldman@leclairryan.com>,
<barany@umn.edu>,
<barany@med.cornell.edu>,
<cnathan@med.cornell.edu>,
<bjk44@cornell.edu>

Date Apr 22, 2017 at 12:49 AM

I have spoken to a contingency law firm that is interested at looking at the options for Cornell and the inventors in this case.

Sent from my iPhone

On Apr 22, 2017, at 12:27 AM, Monib Zirvi <matzirvi@yahoo.com> wrote:

Search this Illumina publication for
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TTTGATCGTAGCCGGTATGCGACGG

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Sent from my iPhone

Subject Private & Confidential Re: Not one, but two

From Francis Barany <barany@med.cornell.edu>

To: Monib Zirvi <matzirvi@yahoo.com>, Valerie Cross <vlc1@cornell.edu>, rphammer@gmail.com <rphammer@gmail.com>, lubingenetics@me.com <lubingenetics@me.com>, mpearson@akingump.com <mpearson@akingump.com>, maria.kempe@med.lu.se <maria.kempe@med.lu.se>, James R. Kahn <jkahn@med.cornell.edu>, Michael Goldman <michael.goldman@leclairryan.com>, George Barany <barany@umn.edu>, Carl F. Nathan <cnathan@med.cornell.edu>, bjk44@cornell.edu <bjk44@cornell.edu>

Date Apr 22, 2017 at 8:21 AM

Dear Monib, fellow inventors, Matthew P., and Cornell Team,

Monib - excellent sleuthing.

In fact, BOTH sequences listed are from the 16 Barany/Zirvi zip-codes.

(Illumina adds an extra “T” base on the 5’ end — this is an insignificant and inconsequential addition).

The probability that they would pick thees two sequences randomly is: 7.9 x 10 ee 28th — or essentially the same as 1 in the total number of stars in the universe. In other words — impossible.

Inventors, in order that I do not inadvertently violate

privilege I will communicate with Valerie and the Cornell Team privately. I do hope that you trust that I am trying my best to represent all the inventors

I am trying my best to represent all the inventors interests.

But now, I need to run some errands and then go to the March for Science (NYC).

Best,

Francis

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

> On Apr 22, 2017, at 12:27 AM, Monib Zirvi <matzirvi@yahoo.com> wrote:
>
> Search this Illumina publication for
> This Barany/Zirvi Zipcode:
>
> TTTGATCGTAGCCGGTATGCGACGG
>
> Sent from my iPhone
> <bc060012v.pdf>
>
> View less

Subject Re: Private & Confidential Re: Not one, but two

From Maria Kempe <maria.kempe@med.lu.se>

To: Francis Barany <barany@med.cornell.edu>

Cc: Monib Zirvi <matzirvi@yahoo.com>, Valerie Cross <vlc1@cornell.edu>, rphammer@gmail.com <rphammer@gmail.com>, lubingenetics@me.com <lubingenetics@me.com>, mpearson@akingump.com <mpearson@akingump.com>, James R. Kahn <jkahn@med.cornell.edu>, Michael Goldman <michael.goldman@leclairryan.com>, George Barany <barany@umn.edu>, Carl F. Nathan <cnathan@med.cornell.edu>, bjk44@cornell.edu <bjk44@cornell.edu>

Date Apr 22, 2017 at 10:11 AM

Dear All,

Thanks for the call yesterday.
Francis: you have my full trust.
Monib: thanks for your great efforts and input, they are appreciated.

Best regards,
Maria

Sent from my iPad

On 22 Apr 2017, at 14:21, Francis Barany <barany@med.cornell.edu> wrote:

> Dear Monib, fellow inventors, Matthew P., and Cornell Team,
>
> Monib, excellent sleuthing

Monib - excellent sleuthing.

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Francis

[redacted]
barany@med.cornell.edu

[redacted]

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<Synthetic Modification Silica Beads Illumina
2006_Table1.tiff>

Subject Re: Private & Confidential Re: Not one, but two

From Monib Zirvi <matzirvi@yahoo.com>

To: Maria Kempe <maria.kempe@med.lu.se>

Cc: Francis Barany <barany@med.cornell.edu>, Valerie Cross <vlc1@cornell.edu>, rphammer@gmail.com <rphammer@gmail.com>, lubingenetics@me.com <lubingenetics@me.com>, mpearson@akingump.com <mpearson@akingump.com>, James R. Kahn <jkahn@med.cornell.edu>, Michael Goldman <michael.goldman@leclairryan.com>, George Barany <barany@umn.edu>, Carl F. Nathan <cnathan@med.cornell.edu>, bjk44@cornell.edu <bjk44@cornell.edu>

Date Apr 22, 2017 at 10:16 AM

Thank you Maria.

Monib

Sent from my iPhone

On Apr 22, 2017, at 10:11 AM, Maria Kempe <maria.kempe@med.lu.se> wrote:

Dear All,

Thanks for the call yesterday.
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Best regards,
Maria

Sent from my iPad

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<barany@med.cornell.edu> wrote:

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> Monib - excellent sleuthing.
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> But now, I need to run some errands and then go to the March for Science (NYC).
>
> Best,
>
> Francis
>
> [redacted]
> barany@med.cornell.edu
>
> [redacted]
>
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<bc060012v.pdf>

<Synthetic Modification Silica Beads Illumina
2006_Table1.tiff>

View less

Subject Re: Private & Confidential Re: Not one, not two, but four

From Francis Barany <barany@med.cornell.edu>

To: Maria Kempe <maria.kempe@med.lu.se>, Monib Zirvi <matzirvi@yahoo.com>, Valerie Cross <vlc1@cornell.edu>, rphammer@gmail.com <rphammer@gmail.com>, lubingenetics@me.com <lubingenetics@me.com>, mpearson@akingump.com <mpearson@akingump.com>, James R. Kahn <jkahn@med.cornell.edu>, Michael Goldman <michael.goldman@leclairryan.com>, George Barany <barany@umn.edu>, Carl F. Nathan <cnathan@med.cornell.edu>, bjk44@cornell.edu <bjk44@cornell.edu>

Date Apr 22, 2017 at 7:08 PM

Dear Team,

Monib found another document from Illumina that contains our zip codes, published in 2004.

A few points to put in perspective:

1. This was a bit harder to find, since the presence of spaces requires a more sophisticated Google Search.

2. Once again, the Steinberg paper copies 2 of our zip codes, probability that they would pick these two sequences randomly is: 7.9 x 10 ee 28th. These zip codes have identical tetramers in positions 1, 2, & 6, thus making them very close in sequence, which is what you want in order to test conditions that

minimize cross-hybridizations — exactly as taught in the '917 patent.

3. The Steinberg 2004 paper picked the FRIST TWO Zipcodes they plagiarized from the Barany/Zirvi set. The Seinberg-Tatmann 2006 paper picked the THIRD and FOURTH Zipcodes. This is not an accident.

4. Maria and George, you may find the chemistry described in these papers interesting, as I do believe you described most of it in the '917 patent application.

(I am also sending a private email to the Cornell only team.)

Best,

Francis

[redacted]
barany@med.cornell.edu

[redacted]

View more

Covalent_attachment_DNA_Beads_Ste…

Gali Steinberg
Katie Stromsborg
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9885 Towne Centre Drive,
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Strategies for Covalent Attachment of DNA to Beads

Received 15 June 2003;
accepted 1 September 2003
Published online 17 February 2004 in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/bip.20006

Abstract: *Several covalent attachment chemistries were tested for the immobilization of DNA onto glass beads. The comparison was based on the ability of these chemistries to produce derivatized beads that give good hybridization signals. Cyanuric chloride, isothiocyanate, nitrophenyl chloroformate, and hydrazone chemistries gave us the best (yet comparable) hybridization signals. We further characterized the cyanuric chloride method for the number of attachment sites, number of hybridizable sites, hybridization kinetics, effect of linker length on hybridization intensity and stability of the derivatized beads.* © 2004 Wiley Periodicals, Inc. Biopolymers 73: 597 605, 2004

Keywords: *covalent attachment; immobilization; DNA: glass beads; hybridization*

INTRODUCTION

DNA array technology uses microscopic arrays of DNA molecules immobilized on solid supports for biomedical analysis of gene expression, polymorphism or mutation detection, DNA sequencing, and gene discovery.[1,2] There are two distinct approaches to manufacturing microarrays. In one approach, DNA can be synthesized directly on the surface.[3,4] This approach provides wide exibility in design of custom arrays without preliminary synthesis of modi ed oligonucleotides. However, in situ synthesis does not allow quality control and puri cation of individual array features, and incomplete phosphoramidite coupling prevents high yields of full-length oligonucleotide probes, especially for longer oligos.

The second approach uses presynthesized oligonucleotides that are either adsorbed to the array surface or are attached covalently through end-group modi - cations that react with functional groups on the solid support.[5 8] A variety of immobilization strategies, including entrapment, adsorption, and chemical binding, have been used to couple nucleic acids to solid supports such as glass, ceramics, silicon, magnetic beads, nylon, polymers, and membranes.[5 12] To maximize stability and to assure that only full-length oligos are attached, we chose to explore methods of covalent attachment through a functional group added during the last step of oligo synthesis.

Illumina s BeadArray technology uses silica microspheres (beads) as the array elements.[13] For genotyping and gene expression applications, each microsphere is derivatized with a particular oligonucleotide that acts as a probe for the complementary sequence in an assay solution. In this article, we compare several covalent attachment chemistries based on their ability to produce derivatized beads that give good hybridization signals. For a particular chemistry, we

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Biopolymers, Vol. 73, 597 605 (2004)
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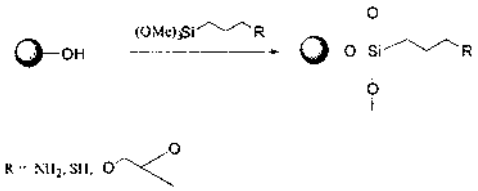


FIGURE 1 General bead silanization scheme.

further characterize the number of attachment sites, the number of hybridizable sites, the hybridization kinetics, the effect of linker length on hybridization intensity, and the stability of derivatized beads.

MATERIALS AND METHODS

Chemical Reagents

Silica beads in water (3 μm diameter, $\sim 5\times10^{10}$ beads/g) were obtained from Bangs Laboratories, Inc., Carmel, IN. Silanization reagents, 3-aminopropyltrimethoxysilane, 3-mercaptopropyltrimethoxysilane, and 3-glycidoxypropyltrimethoxysilane were obtained from United Chemical Technologies (UCT), Bristol, PA. Succinimidyl 4-hydrazinonicotinate acetone hydrazone, and 5′-aldehyde modi ed oligonucleotide 5′-(CHO) TTT GAA AAG CCT ACA CGA CGG CGA A-3′ (capture probe) were obtained from Solulink, San Diego, CA. All other oligonucleotides 5′-NH_2-TTT GAA AAG GGA CGT GCG CTT CGA A-3′ (capture probe), 5′-HS-TTT GAA AAG GGA CGT GCG CTT CGA A-3′ (capture probe), 5′-FAM-TTT CGC CGT CGT GTA GGC TTT TCA A-3′ (target), 5′-FAM-TTT CGA AGC GCA CGT CCC TTT TCA A-3′ (target), were obtained from Operon Technologies, Alameda, CA, or synthesized in house using the Oligator technology. All oligonucleotides were high performance liquid chromatography (HPLC) puri ed. All other reagents were obtained from NovaBiochem, Aldrich or Sigma. All solutions were prepared with OmniPur (sterile, nuclease free) water from Merck.

Surface Modifications

Silanization. The beads were washed with ethanol prior to derivatization with one of the silane reagents (silanization is shown in Figure 1).

Silica beads (1 g) were washed with 10 mL ethanol (HPLC grade). The beads were then suspended in 10 mL ethanol followed by addition of 50 μL (0.5%) silane reagent, and shaken for 1 h at room temperature. Following silanization, they were washed 5 times with 10 mL ethanol and 3 times with 10 mL ether, dried, and stored at room temperature (RT).

Ninhydrin Test. Completion of various reaction steps was monitored (qualitatively) using the ninhydrin test as follows: A small amount of ninhydrin solution (10% by weight ninhydrin in ethanol) was heated to 120°C, a smidgen of beads was added to one test tube, and the other was used as reference. When primary amines were present on the beads, ninhydrin solution turned blue; otherwise, the color of the solution remained unchanged.

Amino (or Thiol) Loading Measurement on Beads. Silanized beads (1 g) were suspended in methylene chloride (10 mL) followed by addition of 200 μL (1.2 mmol) of diisopropyl ethylamine (DIEA). After a brief sonication, 258 mg (1mmol) 9- uorenylmethyl chloroformate (Fmoc Cl) was added into the suspension and the reaction mixture was shaken for 1 h at RT. The beads were washed 5 times with 10 mL methylene chloride and 5 times with 10 mL acetonitrile.

Unreacted amino (or thiol) groups were capped with a mixture of 0.2*M* acetic anhydride and 0.2*M* DIEA in methylene chloride (10 mL for 1 g of beads). The suspension was shaken overnight at RT. The beads were washed 5 times with 10 mL methylene chloride and 5 times with 10 mL acetonitrile.

To estimate available amino groups, the Fmoc protecting group was removed and its absorbance was measured as follows: After capping, the beads (1 g) were suspended in a solution (10 mL) of 20% piperidine in DMF (dimethylformamide) and shaken for 30 min. The beads were then centrifuged, the supernatant was collected and its absorption at 301 nm was measured. The number of reactive groups per bead (i.e., the bead loading) was calculated from

$$C = A/\varepsilon l \quad (C = \text{conc. of Fmoc molecules}, \ \varepsilon = 7800 \text{ for Fmoc at 301nm}) \tag{1a}$$

$$\text{Reactive amino groups/bead} = \text{Fmoc molecules/number of beads} \quad (\text{there are } 5\times10^{10} \text{ beads/g}) \tag{1b}$$

Chemical Modifications of Silanized Beads

Figure 2 shows a general chemical modi cation scheme.

Detailed chemical modi cations carried out on amino silanized beads are shown in Scheme 1.

Scheme 2 shows immobilization of thio-modi ed oligos on thiol-silanized beads.

Scheme 3 shows immobilization of amino-modi ed oligos on glycidoxypropyl- silanized beads.

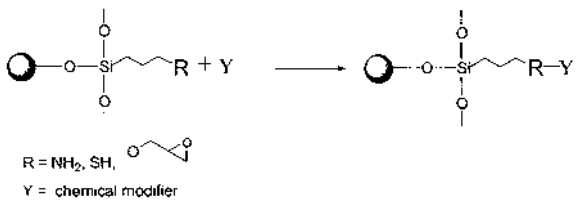
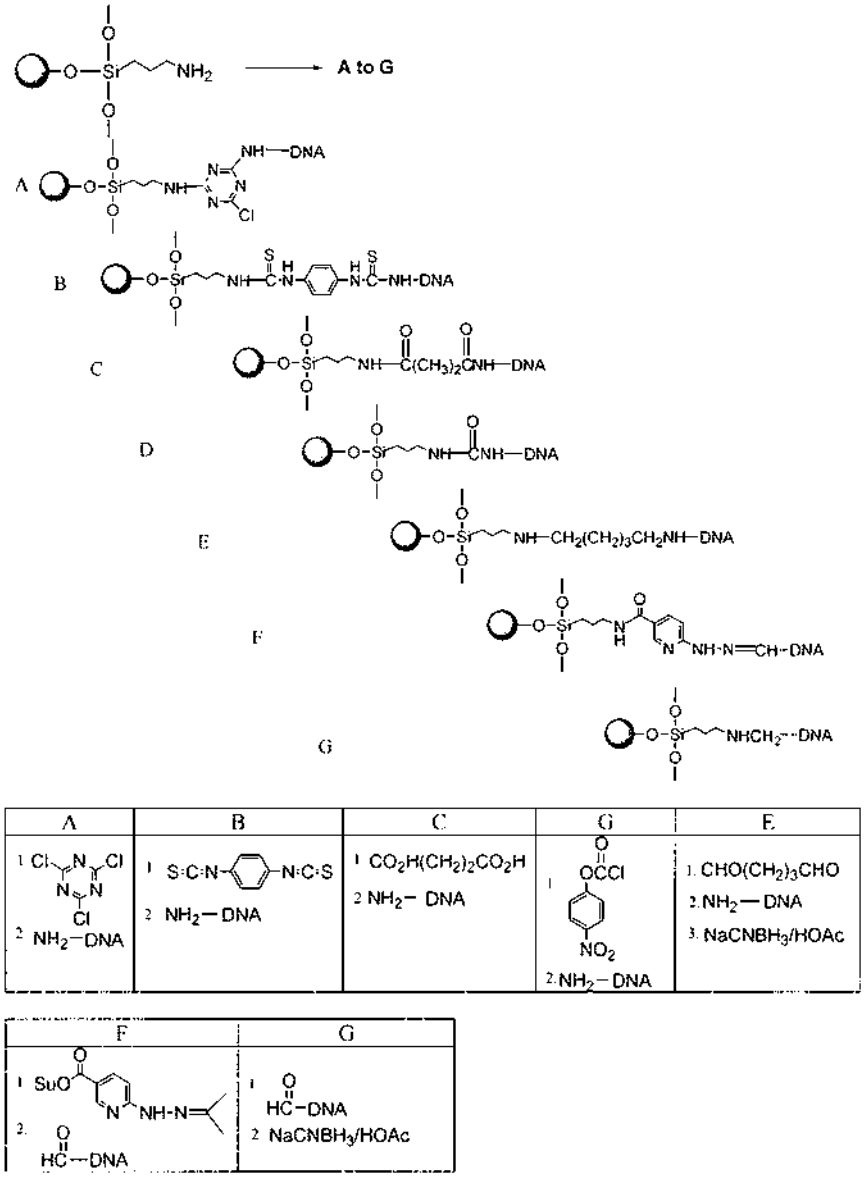
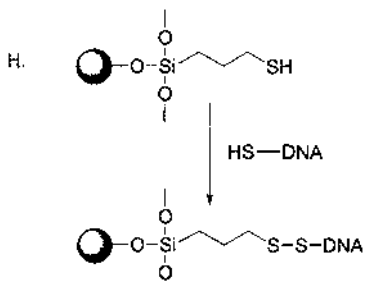


FIGURE 2 General chemical modi cation of silanized beads.



SCHEME 1 Detailed chemical modi cations of amino-silanized beads.

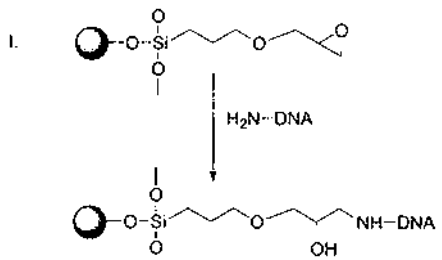
Cyanuric Chloride Activation. Aminopropyl beads (100 mg) were suspended in acetonitrile (1 mL), followed by addition of 20 μL (0.12 mmol) DIEA. After a brief sonication, 10 mg (0.05 mmol) cyanuric chloride was added and the reaction mixture was shaken for 2 h at RT. The beads were washed 3 times with 1 mL acetonitrile and twice with 1 mL 0.05*M* sodium borate buffer (pH 8.5).



SCHEME 2 Immobilization of oligos on thiol beads.

PDITC (1,4-Phenylene Diisothiocyanate) Reaction. Aminopropyl beads (100 mg) were suspended in solution (10% pyridine and 0.2% PDITC in DMF, 1 mL) and shaken for 2 h at RT. The beads were washed 5 times with 1 mL DMF, 3 times with 1 mL ethanol, and 3 times with 1 mL methylene chloride.

Dicarboxylic Acid Reaction. Aminopropyl beads (100 mg) were dispersed in DMF (1 mL) followed by addition of 35 μL DIEA (0.2 mmol). The suspension was sonicated, succinic acid (11.8 mg, 0.1 mmol) was added, followed by



SCHEME 3 Immobilization of oligos on glycidoxypropyl beads.

addition of 52 mg (0.1 mmol) of PyBOP (benzotriazole-1-yl-oxy-tris-pyrrolidinophosphonium hexa uorophosphate). The beads were shaken overnight at RT. They were then washed 3 times with 1 mL DMF, 3 times with 1 mL methylene chloride, and 3 times with 1 mL acetonitrile.

Activation with 4-Nitrophenyl Chloroformate. Aminopropyl beads (100 mg) were dispersed in methylene chloride (1 mL) followed by addition of 20 μL DIEA (0.12 mmol), and 10 mg 4-nitrophenyl chloroformate (0.05 mmol). The beads were shaken for 2 h at RT and washed 5 times with 1 mL methylene chloride then 5 times with 1 mL acetonitrile.

Dialdehyde Reaction. Aminopropyl beads (100 mg) were dispersed in trimethyl orthoformate (TMOF) (1 mL), followed by addition of 5 mg glutaraldehyde (0.05 mmol). The beads were shaken for 30 min at RT and then washed 3 times with 1 mL DMF and 3 times with 1 mL ethanol.

Reactions with Hydrazones. Aminopropyl beads (100 mg) were dispersed in 1 mL buffer (100 m*M* sodium phosphate, 150 m*M* NaCl, 1 m*M* EDTA, pH 7.3), followed by addition of 8.6 mg succinimidyl 4-hydrazinonicotinate acetone hydrazone (SANH) (0.03 mmol) in 80 μL DMF. The suspension was shaken overnight and the beads were washed 2 times with 1 mL of the aforementioned buffer, and 2 times with 1 mL water. They were nally washed 2 times with 1 mL 0.1*M* sodium acetate buffer (pH 5.1) to deprotect the hydrazine.

Oligo Immobilization

A general oligo immobilization scheme is shown in Figure 3.

General Method for Oligo Immobilization. HPLC-puri ed oligonucleotides (100 nmol in 0.05M sodium borate buffer, pH 8.5) were added to 2M sodium chloride solution (100 μl). The oligo-NaCl solution was added to activated beads (25 mg beads in 100 μl 0.05M sodium borate buffer, pH 8.5). The beads were shaken overnight, then washed 3 times with OmniPur water.

This immobilization method was directly applicable to activated beads from Scheme 1A, 1B, 1D, and Scheme 2. Immobilization of oligonucleotides onto other activated beads was done with slight modi cations to the general method.

For beads coupled to dicarboxylic acid (Scheme 1C), 1*M* EDC solution [1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride] was added during immobilization, to a nal concentration of 100 m*M* EDC.

For beads coupled to aldehydes or dialdehydes (Scheme 1E, Scheme 1G), the immobilization itself was unchanged, but after it was complete, the unstable imine bond(s) were reduced to amine bond(s), as follows: Immediately following immobilization and washings, the beads (100 mg) were dispersed in 1 mL TMOF (trimethyl orthoformate), and a solution of sodium cyanoborohydride (3.4 mg, 0.054 mmol) in 100 μL TMOF was added. The pH was then adjusted using acetic acid (~90 μL) to between 5 and 6. The suspension was shaken for 10 min, and the beads were washed 2 times with 1 mL DMF, 2 times with 1 mL methanol, 2 times with 1 mL 10% triethylamine in methylene chloride, and nally 2 times with 1 mL methanol.

For beads coupled to hydrazones (Scheme 1F), the immobilization procedure was carried out either in 0.05*M* sodium borate buffer, pH 8.5 (as previously described) or under acidic conditions, in sodium acetate buffer, pH 4.7.

For beads silanized with glycidoxypropyltrimethoxysilane (Scheme 3), 1*M* potassium hydroxide solution was added during immobilization, to a nal concentration of 100 m*M* potassium hydroxide. Alternatively, Lewis acid catalyst such as zinc chloride (5 mg) was added instead of potassium hydroxide.

Determination of Capture Probe Loading ef ciency 3′-Fmoc-modi ed 5′-amino-modi ed oligonucleotides were immobilized onto activated beads (25 100 mg), using cyanuric chloride chemistry as described above. After washing the beads with OmniPur water, 1 mL of 20% piperidine in DMF was added to the beads and the bead solution was shaken for 30 min. After centrifugation, the supernatant was collected and uv absorption was measured at 301 nm. The number of oligonucleotides on a bead was calculated using Eq. (1) as previously described. Figure 4 shows how the determination of capture probe loading ef ciency was done.

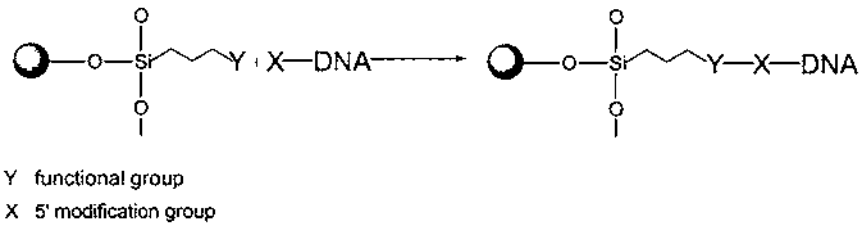


FIGURE 3 A general oligo immobilization scheme.

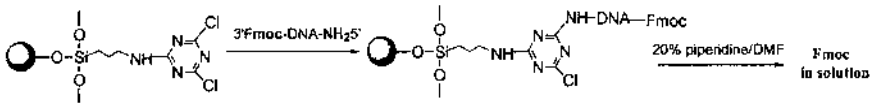


FIGURE 4 Determination of capture probe loading ef ciency.

Complementary Oligonucleotide (Target) Hybridization. Hybridization of complementary oligo (target) to beads containing immobilized probes was carried out in solution and uorescence-activated cell sorter (FACS) was used to measure hybridization intensity.

Hybridization was done in solution as follows: about 1 mg of probe-immobilized beads were suspended in 30 μL hybridization buffer (0.1*M* potassium phosphate, 1*M* sodium chloride, 0.1% Tween-20, and 5% ethanol, pH 7.6), followed by addition of 15 20 μL of ~1 m*M* target (in 0.05*M* borate buffer, pH 8.5) and then shaken for 2 h. The beads were washed 2 3 times with hybridization buffer to remove excess target oligonucleotides. For the release of target from the beads, the beads were incubated with 50 μL of 0.1*M* sodium hydroxide solution for 10 min.

Detection of Hybridization

Fluorescence Activated Cell Sorter. Hybridization in solution was measured with a FACS instrument (Becton Dickinson Biosciences). We used constant laser power of 15 mW, and photomultiplier tube (PMT) gain of 659 for all measurements. Following hybridization in solution (described in the previous section), a small amount of beads was added to 1 mL OmniPur water (in FACS compatible test tube), and average uorescence intensity was recorded for at least 10,000 beads.

Determination of Hybridization Ef ciency. Ten milligrams of beads with immobilized oligonucleotides (capture probe) were hybridized with 50 μL of 1 m*M* uorescein-labeled complementary oligonucleotide (target) at room temperature for 1 h. After washing 10 times with OmniPur water, to remove excess target, the beads were incubated with 100 μL of 0.1*M* NaOH for 10 min. After centrifugation, the solution was collected and diluted to a total volume of 1 mL with hybridization buffer. The uorescence of the above solution was measured using a uorometer (Perkin Elmer, Luminescence spectrometer LS50B). A standard uorescence curve was established using different concentrations of a known amount of complementary oligonucleotide (target). The amount of dye-labeled oligonucleotide was then determined using that standard curve. This process is depicted in Figure 5.

Hybridization ef ciency was calculated from Equation 2:

$$\text{hybridization efficiency} = \frac{\text{amount of dye labeled oligos(target)}}{\text{amount of probes on bead(probe)}}$$

RESULTS AND DISCUSSION

Covalent Immobilization of Capture Probe

The performance of the immobilization schemes was determined based on functional results, by measuring uorescence intensity from target oligo (uorescein modi ed) following hybridization to probe-functionalized beads. Maximal hybridization ef ciencies or oligo loading were not investigated for each of the chemistries as separate entities. When choosing the optimal chemistry for bead arrays, we were more interested in hybridization intensities. All hybridizations were carried out in solution and detection was performed with FACS. Two different sequences (probes) were immobilized on the beads, and results of their hybridization are summarized in two separate tables. Results from immobilization of sequence 6 are summarized in Table I, and results from immobilization of sequence 5 are summarized in Table II.

All experiments (synthesis and immobilizations) were done in triplicate and the numbers (in tables) represent an average of these three readings.

Results in Table I and Table II show that four of the chemistry approaches give equally good hybridization intensities, within experimental errors: cyanuric chloride chemistry (Scheme 1A), diisothiocyanate chemistry (Scheme 1B), nitrophenyl chloroformate chemistry (Scheme 1D), and hydrazone chemistry (Scheme 1F).

Any of these four chemistry approaches can be used. All experiments and measurements described

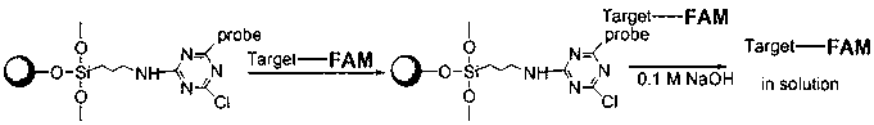


FIGURE 5 Determination of hybridization ef ciency.

Table I Hybridization Results (on FACS) Using Probe Sequence 6 (Probe is Sequence 6: 5′-L-TTT GAA AAG GGA CGT GCG CTT CGA A-3′)

Chemistry	Scheme 1A	Scheme 1B	Scheme 1C	Scheme 1D	Scheme 1E	Scheme 2	Scheme 3
Counts	3500	3400	2700	3500	2300	1500	250
SD	200	210	247	215	198	130	17

below were performed using cyanuric chloride chemistry.

Effect of Spacers on Hybridization Intensity

In theory, the more an immobilized oligonucleotide is spatially removed from the solid support, the closer it is to the solution state and the more likely it is to react freely with complementary oligonucleotides. To assess the in uence of spacers of different length on hybridization properties of immobilized nucleotides, we used polyethylene glycol (PEG) linkers of varying length. The results of hybridizations to these spacer-containing beads are shown in Figure 6.. It appears that the hybridization signal is not affected by the presence of spacer molecules.

Bead Stability

Stability of the probe-immobilized beads, using cyanuric chloride activation, was tested over a period of ve months. During that time period the beads were stored in ethanol at −20°C. At each time point, aliquots of the beads were loaded on three ber bundles and hybridized with the target for 10 min. After washing with hybridization buffer (to remove excess target) hybridization intensities were recorded using a CCD imaging system.[14] Results of this stability experiment are summarized in Figure 7. Hybridization intensities were very consistent and did not show any signi cant changes over the ve-month period.

Oligo Loading Optimization

To determine the number of amino sites available for probe immobilization, the beads were silanized by an increasing concentration of silanization reagent: from 5×10^{-4} to 10%. The number of reactive amino sites measured was strongly dependent on the reactivity of 9- uorenylmethyl chloroformate (see Materials and Methods for clari cation). To obtain consistent results, a very dry reagent must be used. As the concentration of silanization reagent was increased from 5×10^{-4} to 1%, the amount of reactive amino sites grew, reaching a plateau at about 0.5% silanization reagent of 6×10^{7} amino sites per bead (Figure 8). Increasing concentration of silanization reagent past 1% did not increase further the number of amino sites per bead. Oligo loading was measured using covalent attachment of 3′-Fmoc-modi ed 5′-amino-modi ed oligonucleotides to the beads, as described in Materials and Methods. Calculations show that $0.63\times10^{6} \mp 0.086\times10^{6}$ probes per bead were immobilized. Even when >100 times excess probes were used relative to the number of available reactive amino sites, the number of probes per bead did not increase. Thus, there are many amino sites that remain unreacted, suggesting that the limitations of oligonucleotide immobilization are a result of steric hindrance and not a lack of reactive amino sites.

Table II Hybridization Results (on FACS) Using Probe Sequence 5 (Probe is Sequence 5: 5′-L-TTT GAA AAG CCT ACA CGA CGG CGA A-3′)

Chemistry	Scheme 1A	Scheme 1F	Scheme 1G
Counts	3400	4000	1900
SD	241	300	176

Packing Density

Packing density, at the point of optimal hybridization, was determined from the number of probes measured

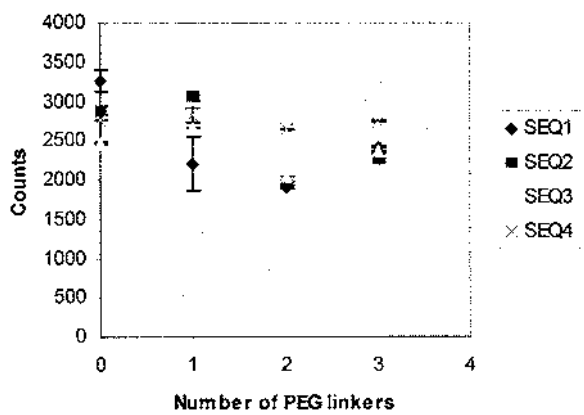


FIGURE 6 Effect of linkers on hybridization intensities of four random 25-mer oligonucleotides attached to the beads.

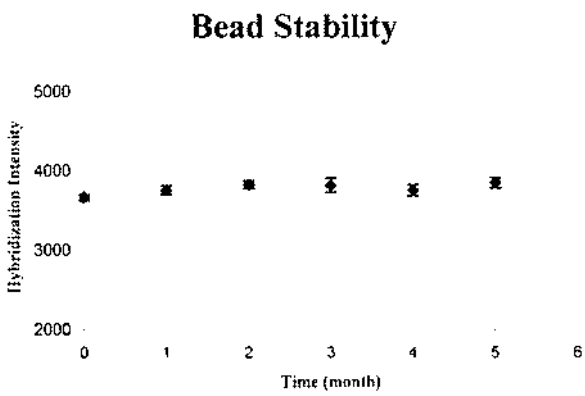


FIGURE 7 Bead stability with time: (1) Beads with oligo attached were stored in EtOH at −20°C. (2) At each time period, three ber arrays were assembled and tested by hybrization. (3) Dyed beads were used to calibrate the intensity of the system. (4) During the ve-month testing period, the coef cient variation (CV) of hybridization intensity was less than 10%.

at that point. As discussed in the previous section, there are 0.6×10^6 probes per bead. The surface area of our beads, which are 3 μm in diameter, is

$$SA = 4\pi r^2 = 4\pi(1.5\times10^{-6}\ \text{m})^2 = 2.8\times10^{-11}\ \text{m}^2$$

$$0.6\times10^6\ \text{probes}/2.8\times10^{-11}\ \text{m}^2$$
$$= 2.1\times10^{16}\ \text{probes/m}^2 = 2.1\times10^4\ \text{probes}/\mu\text{m}^2$$

The number of probes in one μm of linear distance can be calculated by taking the square root of the probes/μm^2:

$$(2.1\times10^4\ \text{probes}/\mu\text{m}^2)^{1/2}$$
$$= 146\ \text{probes}/\mu\text{m(or 0.0146 probes/A°)}$$

The center-to-center distance between two probes is therefore 1/0.0146 or 69 Å. This packing density is at the limit of our packing capacity if we consider the fact that the length of our probes (25-mer oligonucleotides) plus the silanization reagent and cyanuric chloride molecules easily add up to 90 Å. If the packing density is any higher, the probes will interfere with each other and hybridization ef ciency will drastically decline. In our case we have a multilayer network of silanization reagent on the bead, which creates a rough surface. This allows the probes to be separated more than in the case of a smooth surface, thus resulting in a greater packing density than available on a smooth surface.

Hybridization Efficiency

Packing density of the DNA capture probe is expected to be an important parameter affecting hybridization intensities. A low surface coverage would presumably yield a low hybridization signal. Conversely, high surface densities might result in steric interference between the covalently immobilized probes, impeding access to the target DNA strand. In principle, surface density is a measure of the number of probes immobilized per μm^2. However, packing density can also be correlated to the number of reactive amino sites on the bead (although not directly). The amount of reactive amino sites per bead can be controlled by varying the concentration of silanization reagent used. To evaluate surface densities and resulting hybridization ef ciencies, we chose to alter the amount of bead silanization (i.e., amount of reactive amino sites) and follow the changes in hybridization intensities. Hybridization intensity is a product of two effects, packing density and hybridization ef ciency, which are interdependent. Our goal was to nd the point where the combination of these two gave the highest hybridization intensity.

It appears that optimal hybridization is observed when 0.005 1% silanization reagent was used, corresponding to 4×10^6 8×10^7 reactive amino sites (Figure 9). We chose to use 0.5% silanization reagent for subsequent synthesis. The number of oligos per bead for 0.5% silanization was determined (see in Materials and Methods, the section on the determination of capture probe loading ef ciency section) to be ~0.63 $\times$ 10^6 $\pm$ 0.086 $\times$ 10^6 oligos per bead.

Hybridization ef ciency was then calculated at 0.5% silanization (with 4×10^6 8×10^7 reactive amino sites available), as previously described in Materials and Methods, determination of hybridization

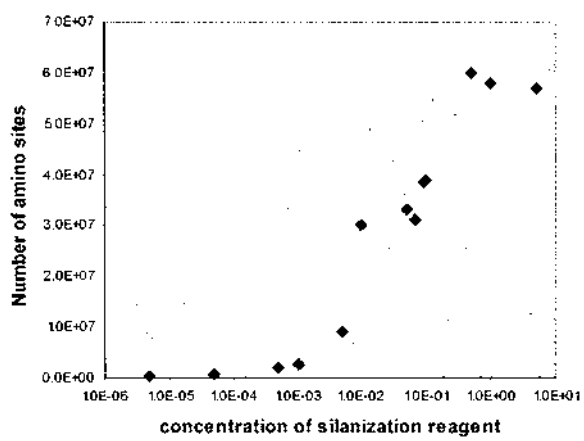


FIGURE 8 Variation in the number of reactive amino sites as a function of concentration of silanization reagent.

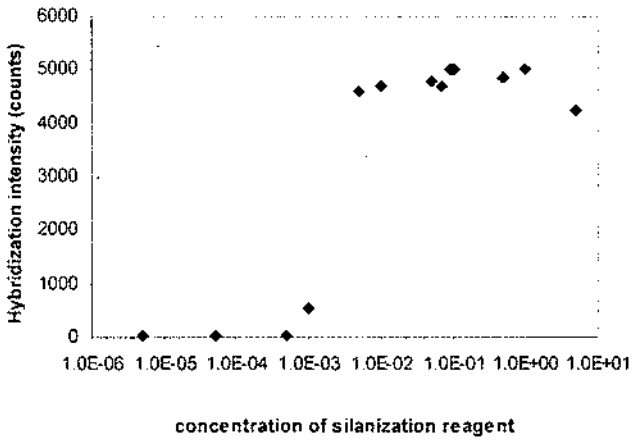


FIGURE 9 Hybrization intensity as a function of concentration of silanization reagent.

ef ciency section. To describe this brie y: once maximum hybridization intensity was achieved, the hybridized beads were incubated with 0.1*M* sodium hydroxide solution for 10 min, and then the absorption of the supernatant was measured at 301 nm. Measurements indicate that there are 0.25×10^6 target oligos hybridized at the point of maximal hybridization intensity. Accordingly, hybridization ef ciency at that point is (0.25×10^6 \$0.6\times10^6$), or about 45%.

CONCLUSION

We evaluated several surface chemistries for use in attaching oligonucleotides covalently to silica beads. Four attachment methods produced derivatized beads that hybridized with high ef ciency to complementary oligos. These were the cyanuric chloride, isothiocyanate, nitrophenyl chloroformate, and hydrazone methods. We chose to optimize the cyanuric chloride chemistry with regards to hybridization intensity. We investigated the stability of the derivatized beads over a ve-month period and found no signi cant change in hybridization intensities. We also investigated the use of PEG spacer molecules to increase the distance of the oligos from the silanized bead surface, potentially reducing steric interference. We found that spacers had no effect on hybridization intensities. These results are in agreement with results obtained by Cantor et al.,[12] who did not observe an improvement in their hybridization ef ciencies when they used a series of poly(dT) sequences as their spacers. They determined that 40% was the maximum hybridization that could be achieved. However, these results contrast with observations by Southern et al.,[15] who found in their system up to 150-fold increase in duplex yield when spacers were inserted between oligonucleotides and a solid support. The discrepancy may be due to several factors, one of which may be the packing density. In our case there is a nominal distance of ~69 Å between probes. However, we use a multilayer silanized surface, so that the actual distance between probes may be greater. Southern et al.[15] calculate about 40 Å between their probes on a at surface. The higher packing density in this case may contribute to reduced hybridization yields, which can be improved by using spacers. The packing density in our experiments may already be optimized and therefore inserting spacers had no signi cant effect on hybridization yields.

It is likely that hybridization ef ciency varies depending on the mode of attachment as well as on packing density. For example, when probes are synthesized directly on the surface (in situ synthesis) many truncated species are synthesized, which do not hybridize. For example, when McGall et al. synthesized 20-mer oligos in situ, they obtained only ~15% yield of full-length oligos and observed hybridization ef ciency of less than 10%.[16] We chose to immobilize full-length, presynthesized oligos and observe a hybridization ef ciency of 45%. Our results are comparable to hybridization ef - ciencies observed by other groups that immobilized presynthesized oligos.[12,17]

The method used here is easily scalable to automated derivatization of beads in bulk. It provides a cost-effective means for manufacturing many thousands of different microarray elements.

We would like to thank Illumina s Bioinformatics group for help with image registration and analysis, the Engineering group for bead array imaging, and the Chemistry group for support and discussion.

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Reviewing Editor: Dr. David A. Case

Subject Re: Private & Confidential Re: Not one, not two, but four

From Monib Zirvi <matzirvi@yahoo.com>

To: Francis Barany <barany@med.cornell.edu>

Cc: Maria Kempe <maria.kempe@med.lu.se>, Valerie Cross <vlc1@cornell.edu>, rphammer@gmail.com <rphammer@gmail.com>, lubingenetics@me.com <lubingenetics@me.com>, mpearson@akingump.com <mpearson@akingump.com>, James R. Kahn <jkahn@med.cornell.edu>, Michael Goldman <michael.goldman@leclairryan.com>, George Barany <barany@umn.edu>, Carl F. Nathan <cnathan@med.cornell.edu>, bjk44@cornell.edu <bjk44@cornell.edu>

Date Apr 22, 2017 at 7:21 PM

Illumina has done this to multiple scientists and when all is done, a class action lawsuit by individual scientists may finally trap them in their lies.

Justice in this case will require strong will and perseverance.

Monib

Sent from my iPhone

On Apr 22, 2017, at 7:08 PM, Francis Barany <barany@med.cornell.edu> wrote:

Dear Team,

Monib found another document from Illumina that contains our zip codes, published in 2004.

A few points to put in perspective:

A few points to put in perspective:

1. This was a bit harder to find, since the presence of spaces requires a more sophisticated Google Search.

2. Once again, the Steinberg paper copies 2 of our zip codes, probability that they would pick these two sequences randomly is: 7.9 x 10 ee 28th. These zip codes have identical tetramers in positions 1, 2, & 6, thus making them very close in sequence, which is what you want in order to test conditions that minimize cross-hybridizations — exactly as taught in the '917 patent.

3. The Steinberg 2004 paper picked the FRIST TWO Zipcodes they plagiarized from the Barany/Zirvi set. The Seinberg-Tatmann 2006 paper picked the THIRD and FOURTH Zipcodes. This is not an accident.

4. Maria and George, you may find the chemistry described in these papers interesting, as I do believe you described most of it in the '917 patent application.

(I am also sending a private email to the Cornell only team.)

Best,

Francis

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

> On Apr 22, 2017, at 10:11 AM, Maria Kempe <maria.kempe@med.lu.se> wrote:
>
> Dear All,

Thanks for the call yesterday.
Francis: you have my full trust.
Monib: thanks for your great efforts and input, they are appreciated.

Best regards,
Maria

Sent from my iPad

On 22 Apr 2017, at 14:21, Francis Barany <barany@med.cornell.edu> wrote:

> Dear Monib, fellow inventors, Matthew P., and Cornell Team,
>
> Monib - excellent sleuthing.
>
> In fact, BOTH sequences listed are from the 16 Barany/Zirvi zip-codes.
>
> (Illumina adds an extra ???T??? base on the 5??? end ??? this is an insignificant and inconsequential addition).
>
> The probability that they would pick thees two sequences randomly is: 7.9 x 10 ee 28th ??? or essentially the same as 1 in the total number of stars in the universe. In other words ??? impossible.
>
> Inventors, in order that I do not inadvertently violate privilege I will communicate with Valerie and the Cornell Team privately. I do hope that you trust that I am trying my best to represent all the inventors interests.
>
> But now, I need to run some errands and then go to the March for Science (NYC).
>
> Best,
>
> Francis
>
> [redacted]
> [redacted]
> barany@med.cornell.edu

barany@med.cornell.edu

[redacted]

On Apr 22, 2017, at 12:27 AM, Monib Zirvi
<matzirvi@yahoo.com> wrote:

Search this Illumina publication for
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<Synthetic Modification Silica Beads Illumina
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Subject Re: Private & Confidential Re: Not one, not two, but four

From George Barany <barany@umn.edu>

To: Francis Barany <barany@med.cornell.edu>

Cc: Maria Kempe <maria.kempe@med.lu.se>, Monib Zirvi <matzirvi@yahoo.com>, Valerie Cross <vlc1@cornell.edu>, rphammer@gmail.com <rphammer@gmail.com>, lubingenetics@me.com <lubingenetics@me.com>, mpearson@akingump.com <mpearson@akingump.com>, James R. Kahn <jkahn@med.cornell.edu>, Michael Goldman <michael.goldman@leclairryan.com>, Carl F. Nathan <cnathan@med.cornell.edu>, bjk44@cornell.edu <bjk44@cornell.edu>

Date Apr 22, 2017 at 7:45 PM

Dear All,

Outstanding detective work.

I took a quick look at the 2003 Steinberg et al. paper that you attached, but am relying on my memory of what we proposed in our program project grant that was reviewed in 1994. At the time of our proposal, we had not carried out any of the chemistry with our own hands, but compiled in one master Scheme a series of precedented conjugation methods from the peptide and protein field (some but not all of which we had personal experience with) that we were confident could eventually be applied to covalently attach DNA oligos to beads and surfaces.

From my perspective as a scientist rather than a lawyer, I think our strongest point of focus should be on the zip code universal array concept, and the multiple "smoking gun" evidence that our teachings

multiple "smoking gun" evidence that our teachings were plagiarized both in the general and in the high specificity.

Best wishes,

GB

On Sat, Apr 22, 2017 at 6:08 PM, Francis Barany <barany@med.cornell.edu> wrote:

> Dear Team,
>
> Monib found another document from Illumina that contains our zip codes, published in 2004.
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> A few points to put in perspective:
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> (I am also sending a private email to the Cornell only team.)
>
> Best,
>
> Francis

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

On Apr 22, 2017, at 10:11 AM, Maria Kempe <maria.kempe@med.lu.se> wrote:

Dear All,

Thanks for the call yesterday.
Francis: you have my full trust.
Monib: thanks for your great efforts and input, they are appreciated.

Best regards,
Maria

Sent from my iPad

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> Monib - excellent sleuthing.
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> Inventors, in order that I do not inadvertently

inventors, in order that I do not inadvertently violate privilege I will communicate with Valerie and the Cornell Team privately. I do hope that you trust that I am trying my best to represent all the inventors interests.

But now, I need to run some errands and then go to the March for Science (NYC).

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[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

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> Sent from my iPhone
> <bc060012v.pdf>

> <Synthetic Modification Silica Beads Illumina 2006_Table1.tiff>

View less

--
George Barany

Distinguished McKnight University Professor of
Chemistry
University of Minnesota
Department of Chemistry
[redacted]

Subject Re: Private & Confidential Re: Not one, not two, but four

From Monib Zirvi <matzirvi@yahoo.com>

To: Francis Barany <barany@med.cornell.edu>

Cc: Maria Kempe <maria.kempe@med.lu.se>, Valerie Cross <vlc1@cornell.edu>, rphammer@gmail.com <rphammer@gmail.com>, lubingenetics@me.com <lubingenetics@me.com>, mpearson@akingump.com <mpearson@akingump.com>, James R. Kahn <jkahn@med.cornell.edu>, Michael Goldman <michael.goldman@leclairryan.com>, George Barany <barany@umn.edu>, Carl F. Nathan <cnathan@med.cornell.edu>, bjk44@cornell.edu <bjk44@cornell.edu>

Date Apr 22, 2017 at 9:57 PM

Steinberg 2006 uses our Zipcodes to create the hybridization and addressing scheme for Infinium arrays.

If you split a Zipcode in half and couple it with a linker to an address, it is still an addressable Universal Zipcode Array.

It is a miscarriage of Justice to let them get away with such a trivial and insubstantial modification which is an obvious attempt to skirt around Barany IP claim language. An person of ordinary skill of the art would see right through this. Scripps will likely have the guts to pursue this for their one patent, it is a tragedy of epic proportions that it appears that we won't get our chance.

Monib Zirvi, MD/PhD
Sent from my iPhone

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<Covalent_attachment_DNA_Beads_Steinberg_2004_M&M.tiff>

View less

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Cc: Maria Kempe <maria.kempe@med.lu.se>, Valerie Cross <vlc1@cornell.edu>, rphammer@gmail.com <rphammer@gmail.com>, lubingenetics@me.com <lubingenetics@me.com>, mpearson@akingump.com <mpearson@akingump.com>, James R. Kahn <jkahn@med.cornell.edu>, Michael Goldman <michael.goldman@leclairryan.com>, George Barany <barany@umn.edu>, Carl F. Nathan <cnathan@med.cornell.edu>, bjk44@cornell.edu <bjk44@cornell.edu>

Date Apr 22, 2017 at 10:16 PM

If the inventors can secure the funding for a trial independent of Cornell and Life Technology, why can't we pursue this to completion?

I'm sure a contingency law firm would seriously consider it.

Monib

Sent from my iPhone

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View less

Subject MonibZirviCornellvIllumina.docx

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To: Valerie Cross Dorn
<vlc1@cornell.edu>,
<rphammer@gmail.com>,
<lubingenetics@me.com>,
<mpearson@akingump.com>,
<maria.kempe@med.lu.se>,
<jkahn@med.cornell.edu>,
<michael.goldman@leclairryan.com>,
<barany@umn.edu>,
<barany@med.cornell.edu>,
<cnathan@med.cornell.edu>,
<bjk44@cornell.edu>

Date Apr 22, 2017 at 10:58 PM

I had written up a declaration that I was going to send to Judge Stark with the help of an attorney. If you can take the time to read it, I would greatly appreciate it.

Sent from my iPhone

MonibZirviCornellvIllumina.docx.pdf

In The
United States District Court
District of Delaware

CORNELL UNIVERSITY, ET AL.
Plaintiffs

v.

ILLUMINA INC.
Defendant

C.A. 1:10-cv-00433-LPS-MPT

MONIB A. ZIRVI
IN SUPPORT OF CORNELL UNIVERSITY,
ET AL.

DECLARATION

I, Monib A Zirvi, declare that I graduated Summa Cum Laude from Princeton University in 1993 with a Degree in Electrical Engineering with special interest in Computer Engineering and a Certificate in Engineering Biology. I was then selected for the Medical Scientist Training Program at the Tri-Institutional M.D./Ph.D. Program at Cornell University Medical College/Memorial Sloan Kettering Cancer Center/Rockefeller University. In 1994, I met Dr. Francis Barany who is currently a Professor of Microbiology at Weill Medicine Cornell.

In February 1994, Dr. Barany had submitted a Program Project Grant Application to the National Cancer Institute entitled, "New Methods for Cancer Detection." In this grant application, detailed designs and concepts for a novel DNA array called the Universal Zipcode Array was laid out in detail. I became intrigued with the possibility of these new approaches to revolutionize the way DNA, the basic code of Life, was analyzed, sequenced and detected. I therefore decided to obtain his Ph.D. in the Laboratory of Dr. Francis Barany.

I graduated with my Ph.D. in 1999 and published an article on "Ligase-based detection of Mononucleotide Repeat Sequences." I then completed my M.D. Degree in 2000 and eventually completed a Dermatology Residency at the Hospital of the University of Pennsylvania. I have been a practicing Physician for years and I have been awarded a number of Awards including Castle Connolly's Top Doctor Award.

One of the initial research projects that I worked on in the laboratory of Dr. Francis Barany, was the synthesis of special artificial DNA sequences called Zipcodes. These consisted of sets of artificial (non-naturally occurring) sequences which were specifically created to decouple the process of hybridization from the detection of sequences in DNA analyses. Prior to this, the state of the art at the time involved synthetic DNA sequences arranged in arrays with the use of pure hybridization to discriminate between two very similar DNA fragments. This was the approach taken by the leader in the DNA array market at the time, Affymetrix. The designs and specifications and uses of Universal Zipcode Arrays were patented in the '917 and '470 Patent families.

Dr. Francis Barany's Grant Proposal in 1994 was reviewed by an NIH Study Section. One of the reviewers on the study section was the then Chief Technology Officer of Affymetrix, Dr. Stephen Fodor, who

took the ideas he learned about during the confidential review of Dr. Barany's Grant application and started using them at Affymetrix. Other employees at Affymetrix at the time included Dr. Mark Chee,

Dr. Jian-Bin Fan and Dr. Kevin Gunderson, all of whom eventually left Affymetrix to join Illumina Inc. when it was founded by Dr. David Walt of Tufts University. Other early employees at Illumina included Dr. John Stuelpnagel.

It is noteworthy to mention that in this present matter before the Court, that when Cornell requested to depose Dr. Mark Chee and Dr. Jian-Bin Fan, Illumina Inc. claimed that "they could not be located," and thus have not been deposed. There are numerous relevant patent applications and other documents submitted under their names, many of which have important unanswered fact disputes regarding inventorship. It has become apparent that Illumina may have misled the Court and Cornell when they stated they did not know where Jian-Bing Fan was. There have been papers and patents with him as a co-author filed with Illumina's knowledge since the start of this case. In addition, an Illumina employee, Xuyu Cai registered the AnchorDx.com website that Jian-Bing Fan used in 2015 to make it appear that he had fled. The head of Market Development for Illumina in China attended a meeting with Jian-Bing Fan in September 2016 in China. Please see Appendix for all of the relevant information regarding this potential Obstruction of Justice and Witness tampering matter.

As noted, Illumina. Inc. was founded in part by Dr. David Walt of Tufts University. Prior to 1995, Dr. Walt had been conducting research in use of fiberoptic bead-based microsensors for detection of volatile small molecules, but not DNA. In 1995, prior to starting Illumina, Inc., Dr. Walt had spoken with Dr. Francis Barany about Dr. Barany's lab research and these discussions included not only descriptions of the concept of a Universal Zipcode Array, but also potential uses of the Zipcode Array including detection of products of ligation reactions. At that time, PCR (polymerase chain reaction) was a well-known method of replicating many copies of a fragment of DNA. LDR, or Ligase Detection Reaction, involved using a thermostable DNA ligase to connect two nearby oligonucleotides and then detecting whether the ligase successfully joined the two oligonucleotides. Thereafter, Dr. Walt changed the focus of his laboratory research both at Tufts and at Illumina, Inc., and began developing commercial products to detect SNPs (single nucleotide polymorphisms) and eventually sequence DNA. There are relevant facts that the Court needs to be aware of regarding this matter. It is also notable that Dr. David Walt was not presented as a witness by Illumina Inc., even though as Chief Scientific Officer and Founder, he would have firsthand knowledge of materially pertinent facts.

Illumina produces randomly assembled bead arrays. A randomly assembled array is not useful until one knows which sequences are at which X and Y positions in a two dimensional array. As Dr. David Walt stated in testimony under oath in the *Syntrix Biosystems, Inc. v. Illumina Inc.* trial in the United States District Court in the Western District of Washington at Tacoma, once the beads were laid out on a silicon or a glass or plastic slide, one of the substrates described in his patent, the arrangement, "would be two dimensional." To define the location of any individual bead would require knowing only two positions, the X value and the Y value. Illumina Inc. claims that Infinium arrays are pure hybridization arrays. However, prior to use, the sequences at a given location must be determined. That is why in their own product literature, it is stated that the user must make sure the DMAP file (which contains the location data) must be in place prior to the analysis. Their "dynamically linked libraries", or DLL files, used to analyze the data in the DMAP files using the DMAP Decode File Client has labeled the sequence IDs at each X value and Y value, "Zipcode." Therefore, it is clear, that they consider that all of the unique "address" sequences that they use to decode or locate their beads are Zipcodes.

It is evident and clearly known by scientists that any given strand of DNA has a complementary sequence. During the initial experiments done at Cornell to demonstrate that Universal Zipcode Arrays work, known Zipcode sequences of 24 bases in length were synthesized and spotted in duplicate on arrays. This demonstrated that the two or more Zipcode sequences were hybridizing to the correct addresses on the array. This is clearly embodied in Example 3 in the '917 Patent. The data is shown in Figure 28 and quantified in Tables 4A and 4B.

I helped conduct some of these experiments and multiple Zipcode sequences and substrates and surfaces and configurations were tested. All of these initial experiments, used fluorescently labeled DNA using only Zipcode sequences and their complements with NO target DNA sequence. Some of these experiments later included the addition of non-Zipcode sequences to a Zipcode sequence prior to attachment on the array. This was one of the ways tested to increase the efficiency of hybridization by creating a larger template for DNA fragments to hybridize to. PCR/LDR products with Zipcodes were also eventually used to combine target and Zipcode sequences. Further, in the '470 Patent family, there are descriptions of embodiments in which composite Zipcodes containing NO target sequence would be captured on Universal Zipcode arrays.

In February 1999, I wrote software in Visual Basic and Microsoft Excel to generate lists of Zipcode sequences. These sequences were generated to have 24 bases in length and have a narrow melting temperature (Tm) range. In addition, each Zipcode sequence in the set differed from other Zipcode sequences in the set by 25% or more. These Zipcode sets were created using a group of 36 tetramers (4 base sequences) with unique properties. One of the copyrighted and eventually patented sequences (US Patents 7455965, 8492085, 9340834) that was generated using this approach was:

TTGAAAAGCCTACACGACGGCGAA

After my deposition in July 2015, I was asked for potential search terms that were materially relevant. This patented 24 base sequence plays a crucial fact role in this case. With the advent of search engines such as Google, these sequences act as a digital fingerprint to detect if Intellectual Property theft or infringement has occurred. If you Google this sequence, Dr. Barany's paper publishing this and other sequences appears in the search results. Surprisingly, a failed Illumina Patent application authored by Dr. Kevin Gunderson and Dr. Mark Chee entitled, "Probes and Decoder Oligonucleotides" also appears. In fact, this is the first entry in Table 2 in this and other Patent application submissions. It is labeled "Illumacode 1" in the initial provisional submission. This is materially relevant to this case as it not only demonstrates plagiarism and infringement of Intellectual Property rights, but also shows that Illumina considers their "Illumacodes" as Zipcodes corroborating the findings in Illumina's DMAP Decode File Client DLL files. These both constitute clear evidence of willful infringement.

In another relevant case, Dr. John Zebala, a former member of the Barany Laboratory founded Syntrix Biosystems, Inc. This company sued Illumina Inc. for willful infringement and the verdict labeled this as an example of more egregious acts of infringement. *See Syntrix Biosystems, Inc. v. Illumina Inc.,* Cause No. 13-5870BHS (W.D. Wash.). Tellingly, one of the first successful commercial products which Illumina used to generate revenues early on was called the Sentrix **Universal** Array Matrix. In this case, Dr. John Zebala had similarly shared confidential Intellectual Property information with Illumina and its employees and they proceeded to attempt to re-patent very similar ideas in their own names in a rapidly thrown together provisional application in February 2000.

Illumina, Inc. and its employees in the same time frame, also

gained access to proprietary intellectual property generated by Dr. Francis Barany and the other inventors in the '917 and '470 patent families. Using this information, Illumina. Inc. and/or its employees made multiple attempts in 1999 and 2000 and beyond to re-patent the ideas of another in a series of rapidly submitted provisional patent applications. These applications when examined together show a clear pattern of recidivism in terms of hand-drawing figures which very closely mimicked and exactly copied in some cases key figures from Dr. Barany's Program Project Grant, Papers and Patents.

In one particularly egregious instance, Dr. Kevin Gunderson and Dr. Mark Chee submitted on May 20, 1999, a provisional application (60/135123) entitled, "Addressing Arrays using Sequence Specific Adapters." In the very first paragraph of this submission, Cornell's WO 97/31256 and **Universal** arrays are clearly mentioned. It is an obvious attempt to re-patent Zipcodes under the guise of "Adapters." Many of these provisional applications were abandoned after multiple rejection letters by the USPTO and WIPO, many of which specifically cited Barany Laboratory Patents and Publications including WO 97/31256 ('917 Patent Family). Tellingly, references to Barany Laboratory Patents and Papers appear to have been deliberately omitted in subsequent follow up applications by Dr. Gunderson and Dr. Chee while at Illumina Inc.

Finally, the focus of my thesis project involved determining which adjacent sequences (with and without gaps), thermo-stable ligases were capable of successfully ligating. To study this, mononucleotide repeat sequences were chosen as a model system. These are naturally occurring repeats, errors in which sometimes contribute to development or progression of Cancers. It was demonstrated using various different length primers (some with deliberate gaps) and templates of varying lengths, that the ligase preferred perfectly matched primers without any gaps, but that significant signal was also generated from a subset of templates that contained gaps (See Tables in Appendix of my Doctoral Dissertation). This fact is also materially relevant to the *Cornell University, et al. v. Illumina Inc.* case.

I feel compelled to "come forward with specific facts showing that there is a genuine issue for trial." *Matsushita* 475 U.S. at 587 (internal quotation marks omitted.) It is clear that the Universal Zipcode Array concept has revolutionized the way DNA is sequenced and SNPs (single nucleotide polymorphisms) are analyzed. This has led to not only a decrease in the cost of DNA analyses but a rapid increase in the efficiency with which these are done. The Universal

Zipcode Array and other important concepts and assays conceived of and developed and proven in the Barany Laboratory in the mid 1990's, as well as exact copyright sequences generated in 1999 have been instrumental in this revolution.

As stated in *Vehicle IP, LLC v. AT&T Mobility, LLC, et al.* in C.A. No. 09-1007-LPS in the United States District Court Delaware (2016):

"The willfulness inquiry asks whether a party engaged in 'conduct warranting enhanced damages,' under 35 U.S.C § 284, behavior the Supreme Court has described as 'willful, wanton, malicious, bad-faith, deliberate, consciously wrongful, flagrant, or [] characteristic of a pirate.' *Halo Elecs., Inc. v. Pulse Elecs., Inc.*, 136 S. Ct. 1923, 1932 (2016). Prevailing on a claim of either indirect or willful infringement requires a patentee to prove, among other things, that an accused infringer acted with a specific intent to infringe. *See id.* at 1933 (willful infringement); *Global-Tech*, 563 U.S. at 765-66 (2011) (indirect infringement)."

Also stated in *Vehicle IP, LLC v. AT&T Mobility, LLC, et al.* in C.A. No. 09-1007-LPS in the United States District Court Delaware (2016):

"The Court will 'draw all reasonable inferences in favor of the nonmoving party'"

It is humbly hoped that these relevant material facts will be duly considered to help ensure that Justice is served in this Case.

I declare that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Respectfully submitted,

Date: _____ *By:* _____

Subject Re: MonibZirviCornellvIllumina.docx

From George Barany <barany@umn.edu>

To: Monib Zirvi <matzirvi@yahoo.com>

Cc: Valerie Cross Dorn <vlc1@cornell.edu>, Bob Hammer <rphammer@gmail.com>, Matthew Lubin <lubingenetics@me.com>, Pearson, Matthew <mpearson@akingump.com>, Maria Kempe <maria.kempe@med.lu.se>, Jim Kahn <jkahn@med.cornell.edu>, Goldman, Michael <michael.goldman@leclairryan.com>, Francis Barany <barany@med.cornell.edu>, Carl F. Nathan <cnathan@med.cornell.edu>, Brian J Kelly <bjk44@cornell.edu>

Date Apr 23, 2017 at 9:30 AM

Dear All,

I have carefully read Monib's declaration, and compared it to my own recollections and understanding of the case. Monib makes numerous compelling points that, in my opinion, should be deeply troubling to any fair-minded judge once called to his or her attention through an appropriate mechanism. It has been explained to me that this is better done by parties with direct standing, which would specifically be Cornell rather than one (or more) of the inventors.

Two more points on which I can comment directly. (1) I distinctly remember Fodor's participation in the site visit that reviewed our program project grant, and the snide way in which, off-the-record, he "damned with faint praise" the chemistry section of the proposal that I was PI on; this may have included the universal array concept. (2) As I revealed to Matthew Pearson's team in preparing for the deposition (you'll have to review the transcript to

see if it actually came up), I played "matchmaker" to introduce Francis to David Walt. I had met Walt when he gave a seminar at the U of M about his

when he gave a seminar at the U of M about his fiber optics connected to the artificial nose project, and realized that there might be common interests and possibilities involving DNA recognition (I don't remember the exact timeline, though I suspect it could be reconstructed fairly easily).

I hope these remarks are helpful, even as we are very short on time with the judge about to conduct a final review of the proposed settlement terms.

Best wishes,

GB

--
George Barany
Distinguished McKnight University Professor of Chemistry
University of Minnesota
Department of Chemistry
[redacted]

View more

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From Monib Zirvi <matzirvi@yahoo.com>

To: George Barany <barany@umn.edu>

Cc: Valerie Cross Dorn <vlc1@cornell.edu>, Bob Hammer <rphammer@gmail.com>, Matthew Lubin <lubingenetics@me.com>, Pearson, Matthew <mpearson@akingump.com>, Maria Kempe <maria.kempe@med.lu.se>, Jim Kahn <jkahn@med.cornell.edu>, Goldman, Michael <michael.goldman@leclairryan.com>, Francis Barany <barany@med.cornell.edu>, Carl F. Nathan <cnathan@med.cornell.edu>, Brian J Kelly <bjk44@cornell.edu>

Date Apr 23, 2017 at 10:00 AM

Dear George,

Thanks for your feedback and input. The origin story is more compelling than ConnectU's claim against Mark Zuckerberg which was depicted in the movie, the Social Network. If Cornell took this to trial and prevailed on Sentrix and GoldenGate alone, the movie and book rights would likely dwarf the settlement.

Monib

Sent from my iPhone

On Apr 23, 2017, at 9:30 AM, George Barany <barany@umn.edu> wrote:

> Dear All,
>
> I have carefully read Monib's declaration, and compared it to my own recollections and understanding of the case. Monib makes
>
> numerous compelling points that, in my opinion, should be deeply troubling to any fair-minded judge once called to his or her attention through an

once called to his or her attention through an appropriate mechanism. It has been explained to me that this is better done by parties with direct standing, which would specifically be Cornell rather than one (or more) of the inventors.

Two more points on which I can comment directly. (1) I distinctly remember Fodor's participation in the site visit that reviewed our program project grant, and the snide way in which, off-the-record, he "damned with faint praise" the chemistry section of the proposal that I was PI on; this may have included the universal array concept. (2) As I revealed to Matthew Pearson's team in preparing for the deposition (you'll have to review the transcript to see if it actually came up), I played "matchmaker" to introduce Francis to David Walt. I had met Walt when he gave a seminar at the U of M about his fiber optics connected to the artificial nose project, and realized that there might be common interests and possibilities involving DNA recognition (I don't remember the exact timeline, though I suspect it could be reconstructed fairly easily).

I hope these remarks are helpful, even as we are very short on time with the judge about to conduct a final review of the proposed settlement terms.

Best wishes,

GB

On Sat, Apr 22, 2017 at 9:58 PM, Monib Zirvi <matzirvi@yahoo.com> wrote:

> I had written up a declaration that I was going to send to Judge Stark with the help of an attorney. If you can take the time to read it, I would greatly appreciate it.
>
> Sent from my iPhone

--
George Barany
Distinguished McKnight University Professor of
Chemistry
University of Minnesota
Department of Chemistry
[redacted]

View less

Subject 1-s2.0-S0027510705000278-main

From Monib Zirvi <matzirvi@yahoo.com>

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Date Apr 23, 2017 at 2:07 PM

Gunderson explicitly referencing Gerry, Barany et al (reference 20) for universal addressable (Zipcode) arrays

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Review

High-throughput SNP genotyping on universal bead arrays

Richard Shen*, Jian-Bing Fan, Derek Campbell, Weihua Chang, Jing Chen, Dennis Doucet, Jo Yeakley, Marina Bibikova, Eliza Wickham Garcia, Celeste McBride, Frank Steemers, Francisco Garcia, Bahram G. Kermani, Kevin Gunderson, Arnold Oliphant

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Abstract

We have developed a flexible, accurate and highly multiplexed SNP genotyping assay for high-throughput genetic analysis of large populations on a bead array platform. The novel genotyping system combines high assay conversion rate and data quality with >1500 multiplexing, and Array of Arrays™ formats. Genotyping assay oligos corresponding to specific SNP sequences are each linked to a unique sequence (address) that can hybridize to its complementary strand on universal arrays. The arrays are made of beads located in microwells of optical fiber bundles (Sentrix® Array Matrix) or silicon slides (Sentrix BeadChip). The optical fiber bundles are further organized into a matrix that matches a 96-well microtiter plate. The arrays on the silicon slides are multi-channel pipette compatible for loading multiple samples onto a single silicon slide. These formats allow many samples to be processed in parallel. This genotyping system enables investigators to generate approximately 300,000 genotypes per day with minimal equipment requirements and greater than 1.6 million genotypes per day in a robotics-assisted process. With a streamlined and comprehensive assay, this system brings a new level of flexibility, throughput, and affordability to genetic research.
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Keywords: SNP; Genotyping; Microarray; BeadArray

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1. Introduction

With the complete sequencing of the human genome [1,2], large numbers of DNA sequence variants, mainly single nucleotide polymorphisms (SNPs) are revealed. As of June 2, 2004, 9,856,125 SNPs have been found in the human genome and deposited to public databases (NCBI dbSNP Build 121). The analysis of SNPs in the human genome may offer the key to understand genetic differences between individuals and disease states, and eventually improve medical treatments by allowing the prediction of genetically related disease risk and drug response. To meet these goals, major international collaborative efforts have been made to carry out large scale genomic studies that require the determination of hundreds of thousands of genotypes performed in many individuals [3,4].

Large-scale genetic epidemiological studies can be done with a genome-wide approach or with a candidate gene approach [5,6]. The scale of SNP genotyping needed for such studies is several orders of magnitude greater than what has been required for conventional family-based linkage mapping. Realizing the vision of comprehensive genome-wide genetic association studies will require a SNP genotyping system that combines very high throughput and accuracy with very low cost per SNP analysis, i.e., to be able to economically genotype large number of SNPs in large sample sets [7,8].

The BeadArray technology described in this study provides a solution to these problems by combining a miniaturized array platform with a high level of assay multiplexing and scalable automation. The system uses a high-density BeadArray technology in combination with an allele-specific extension, adapter ligation and amplification assay protocol that achieves high multiplexing in a fully integrated production environment. In turn, the high level of multiplexing simultaneously lowers the genotyping cost while increasing the throughput through judicious use of materials and automation.

The multiplexed assay detects up to 1536 SNPs in a single DNA sample. Genotyping 96 samples at once, using a single Sentrix Array Matrix, allows an individual researcher to determine up to 150,000 genotype calls simultaneously. Genotyping throughput may be increased proportionately by processing more Sentrix Array Matrices.

2. BeadArray technology and Sentrix Array formats

At the heart of Illumina genotyping products lies a fundamentally different way of building arrays: the random self-assembly of beads into patterned microwell substrates [9,10]. Illumina has used technological advances in both the fiber-optics and microelectronics industries to build substrates containing tens of thousands to many millions of wells across their surfaces. Quantitatively pooled bead libraries are then self-assembled into the etched microwell substrates, resulting in the highest density array platform currently available. To meet the broad range of researchers' needs, Illumina has developed two different Array of Arrays formats, the Sentrix Array Matrix and the Sentrix BeadChip.

The Array Matrix uses fiber-optic bundles containing nearly 50,000 individual light-conducting strands chemically etched to create a 3-μm well at the end of each strand [11]. Bundles are grouped together into a 96-array configuration matching the well spacing of standard microtiter plates (Fig. 1a). This unique format allows users to simultaneously conduct experiments on 96 arrays simultaneously. The diameter of the bundles

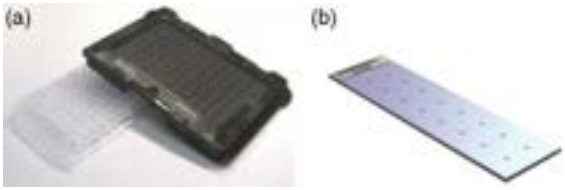

Fig. 1. Two different array of arrays formats: the Sentrix Array Matrix and the Sentrix BeadChip.

is small enough to accommodate a 384-well or 1536-well spacing. Moreover, the platform can be readily incorporated into automated routines using standard robotic equipment, leading to reduced error and human labor requirements.

For users with more moderate throughput requirements, Illumina has introduced the novel BeadChip format (Fig. 1b). This slide-sized platform allows processing of 16 samples at a time, with the same feature-to-feature spacing as standard multi-channel pipettes.

On the Sentrix Array Matrix bundle, up to 1624 unique bead types containing different probe sequences are represented in each array, with an average 30-fold redundancy of each bead type. Independent of the array format, each bead in every array contains hundreds of thousands of covalently attached oligonucleotide probes. After bead assembly into the wells of the array a hybridization-based procedure is used to decode the array, determining which bead type resides in each well. The decoding process is described in detail in a separate publication [12]. This final process validates the performance of each bead type and provides a level of quality control unmatched in the microarray industry. A set of universal bead types is used for the Illumina GoldenGate™ genotyping assay [13]. Each bead type has a unique oligonucleotide sequence, corresponding to the complementary DNA sequences (address sequences) designed into the genotyping assay oligonucleotides. These address sequences hybridize to the universal bead type probes in the last hybridization step of the genotyping assay.

3. GoldenGate genotyping assay

The GoldenGate genotyping assay protocol, illustrated in Fig. 2, allows for a high degree of loci multiplexing in a single reaction through highly specific extension and amplification steps. One of the most important features of the assay is that it genotypes directly on the genomic DNA and does not require prior PCR amplification of the genotyping target.

The DNA sample used in this assay is activated for binding to paramagnetic particles. This activation step is a highly robust process and requires a minimum input of DNA (250 ng at 50 ng/μl). Depending upon the multiplex level, this equates to as low as 0.16 ng of DNA per SNP genotype call. Assay oligonucleotides, hybridization buffer, and paramagnetic particles are then combined with the activated DNA in the assay hybridization step. Three assay oligonucleotides are designed for each SNP locus. Two oligos are specific to each allele of the SNP site, called the allele-specific oligos (ASOs). A third oligo that hybridizes between 1 and 20 bases downstream from the ASO site is the locus-specific oligo (LSO). The 1–20 bp spacing between SNP and LSO allows probe design flexibility to avoid "bad" sequences flanking the SNP or neighboring SNPs. All three oligonucleotide sequences contain regions of genomic complementarity and universal PCR primer sites; the LSO also contains a unique address sequence complementary to a particular bead type. Up to 1536 SNPs may be interrogated simultaneously in this manner. During the hybridization process, the assay oligonucleotides hybridize to the genomic DNA sample bound to paramagnetic particles. Because hybridization occurs prior to any amplification steps, no amplification bias can be introduced into the assay.

Following hybridization, several wash steps are performed, significantly reducing the noise level in the genotyping assay, as properly hybridized assay oligonucleotides are retained and mishybridized and excess assay oligonucleotides are washed away. After oligo hybridization, a polymerase with high specificity for 3′ match is added and only extends the ASO(s) that perfectly match the target sequence at the SNP sites. As the polymerase used has no strand displacement or exonuclease activity, the polymerase fills the gap between the ASO and LSO. When it reaches the LSO the polymerase simply drops off the genomic DNA. High locus specificity is achieved by the requirement that both the ASO and LSO oligos need to hybridize to the same target site. A DNA ligase seals the nick between the extended sequence of the ASO and the LSO to form PCR templates that can be amplified with universal PCR primers. Typically, over 1536 loci on

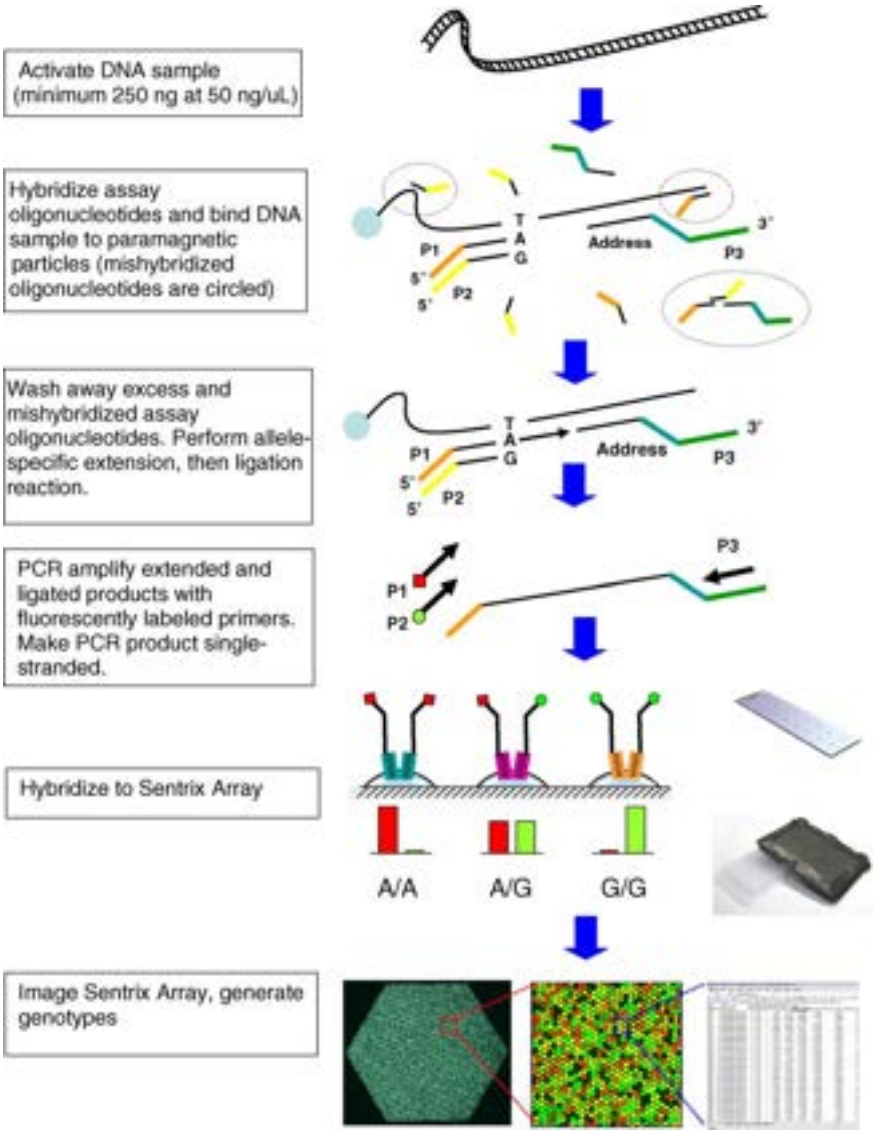

Fig. 2. Illustration of the GoldenGate genotyping assay process.

the genomic DNA are being interrogated simultaneously, and as such a population of over 4600 distinct oligos are present in the reaction tube. Extension of the appropriate ASO and ligation of the extended product to the LSO joins information about the genotype present at the SNP site to the address sequence on LSO. These joined, full-length products provide a template for PCR using only three universal PCR primers P1, P2, and P3.

Universal PCR primers P1 and P2 are labeled with Cy3 and Cy5 dyes, respectively. After thermal cycling and downstream-processing the single-stranded, dye-labeled DNA products (the GoldenGate assay products) are hybridized to their complement bead type through their unique address sequences. Hybridization of the GoldenGate assay products onto the Sentrix Arrays allows for the readout of the highly multiplexed SNP genotyping assay. After the hybridization, the

BeadArray Reader [11] is used to analyze fluorescence signal on the Array Matrix or BeadChip.

Illumina's BeadArray Reader simultaneously scans Sentrix Arrays at two different wavelengths with submicron resolution. A scan of 96 hybridized samples in a Sentrix Array Matrix, representing data acquisition from over 4.5 million discrete beads, takes approximately 90 min. This represents the highest throughput at the highest resolution of any scanning platform used for microarray-based genetic analysis applications.

The BeadArray Reader offers broad dynamic range, high sensitivity, and a low limit of detection. The BeadArray Reader automatically scans an array and uses information from a bead map file (unique to each array) to extract intensity information at 550 and 630 nm wavelengths for each bead type.

The GoldenGate genotyping platform offers flexibility and scalability. The ability to use either the Sentrix BeadChip or the Sentrix Array Matrix allows the user to perform as few as 6000 genotype calls (384 loci multiplex on a 16-sample BeadChip), to as many as 300,000 genotype calls (1536 loci multiplex on two 96-sample Array Matrices) in a single day with minimal equipment requirements. Automating the GoldenGate assay with a few liquid handling robots and a laboratory information management system allows throughput of over 1.6 million genotype calls per day.

4. Oligonucleotide design and synthesis

Quality oligonucleotides are necessary to meet the performance specifications of the GoldenGate assay. Illumina's Oligator® DNA synthesis technology enables parallel synthesis of many plates of oligonucleotides, providing the throughput and quality necessary to support our genotyping products.

Proper design of the assay oligonucleotides is one factor that significantly contributes to the success of the genotyping assay. Our proprietary OligoDesigner software is optimized for the design of GoldenGate assay probes. It evaluates sequences flanking the targeted SNP such as repeated sequences across the genome; palindromic sequences; GC and AT content; neighboring polymorphisms. The allele-specific sequence is designed at T_m of 60 °C (57–62 °C), while the locus-specific probe is designed at T_m of 57 °C (54–60 °C).

Illumina has experience with the design of many hundreds of thousands of GoldenGate genotyping assays and have incorporated this experience into the OligoDesigner software. The customer supplies SNPs along with flanking DNA sequences to Illumina, then these SNPs are entered into the OligoDesigner software, and a file containing the oligo designs and scoring information about the likelihood of success for that design is returned to the user. The user then has the option of selecting which SNP designs to order or can repeat the process with additional SNPs.

5. Contamination control safeguards

Two aspects of contamination control are designed into the genotyping assay: the first detects contamination; the other assists in removal of the contamination source should it occur. For contamination detection, one of four PCR contamination detection controls is added to each tube of assay oligonucleotide pools. When a single assay oligo pool is run, it is expected that only a single contamination control type should have high signal. Should two or more contamination control types have high signal, then significant contamination may have occurred.

The genotyping assay uses dUTP instead of dTTP in the PCR amplification, so that PCR carry-over contamination can be rendered inactive by the use of uracil DNA glycosylase (UDG) [14]. UDG cleaves the uracil base from the phosphodiester backbone of uracil-containing DNA, but has no effect on thymine-containing DNA. True PCR templates generated through the genotyping assay will contain only thymine and no uracil nucleotides.

6. Automatic genotype scoring

The automatic calling of genotypes is performed by genotype calling software (GenCall) genotyping software, using a Bayesian model. GenCall also assigns a confidence score, bound between 0 and 1 to each genotype call. In order to make the calls and assign the corresponding scores, GenCall software creates a locus-specific variables file (LSV). These variables are extracted by a proprietary custom-designed clustering algorithm on a population of DNA's. The advantage of

the custom-designed clustering algorithm over the classical clustering algorithms, e.g., hierarchical clustering or *K*-means, is the incorporation of genotyping-specific heuristics into the energy function of the optimization. This expected improvement is on the basis of Bayesian modeling, which states that when domain-specific knowledge (a.k.a., prior information) are available, one could enhance the outcomes by incorporating them into the model. In other words, the integration of likelihood (i.e., the fit of the data to the model) and prior probability (the domain knowledge) to form posterior probability contains more information than just the likelihood.

The expected clusters are A/A, A/B, and B/B. Often times, due to small minor-allele frequencies, one homozygote cluster or one homozygote and the heterozygote clusters are not present. In such cases, the clustering algorithm in GenCall computes the location and the form of the missing clusters using an artificial neural network.

A quality score, the GenCall score, is calculated for each SNP call, reflecting the degree of separation between homozygote and heterozygote clusters for that SNP and the placement of the individual call within a cluster. To make a genotype call, the software looks at many factors but one of the first is the distribution of beads of the same type and in this way outliers are rejected to ensure genotyping accuracy. The GenCall score is composed of various sub-scores, of which the most important one is the clustering score. This score is a locus-specific score, and is computed by a fuzzy

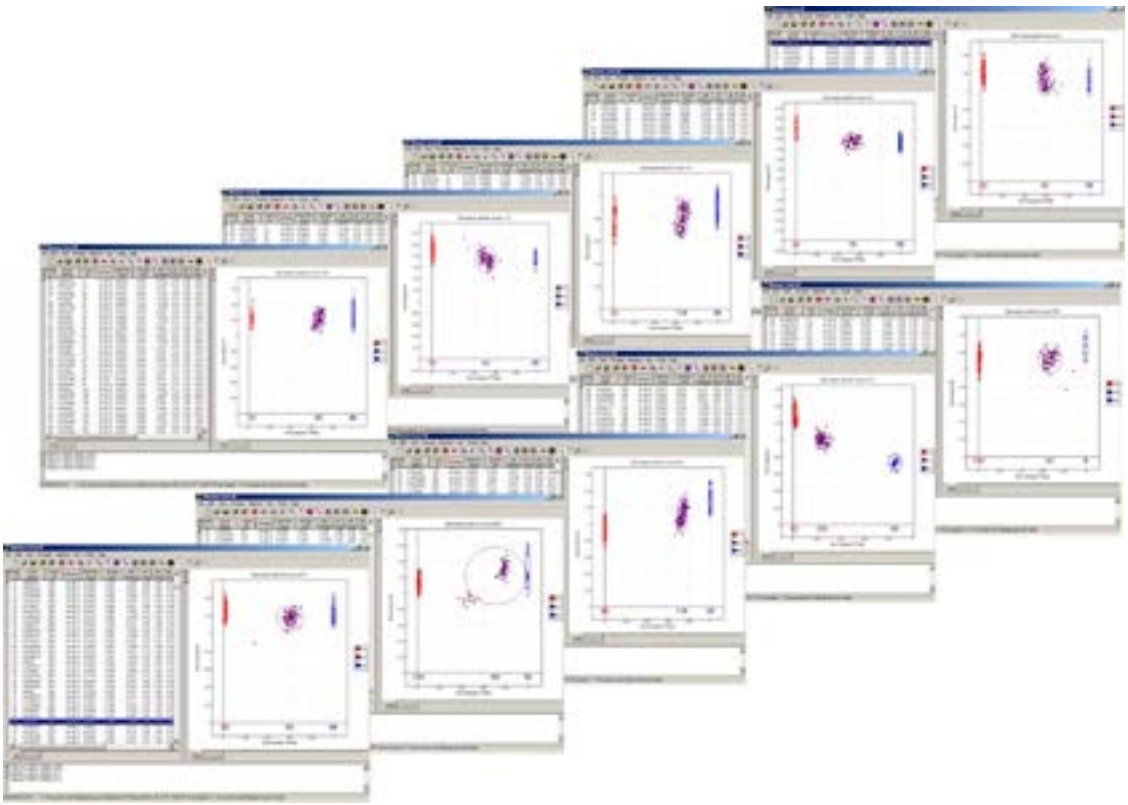

Fig. 3. GenCall software-produced plots of 10 randomly selected loci of 192 samples in polar coordinate representation. Ninety-six DNA samples were run in duplicate (a total of 192 DNAs) across 1263 loci. Each image is a graph of a single locus with 192 “dots” representing individual DNA samples. The *y*-axis is normalized intensity (sum of intensities of the two channels) and the *x*-axis is the “theta” value. Theta values near 0 (left side of graph) are homozygotes for allele “A” and theta values near 1 (right side of graph) are homozygotes for allele “B”. The GenCall software has also automatically grouped the 192 DNAs for each locus into the two homozygote clusters (red and blue) and the heterozygote cluster (purple).

logic inference system. It varies from 0.0 to 1.0, and correlates with accuracy of the genotype call. GenCall scores have been shown to correlate with the accuracy of the genotyping call [13,15].

Figs. 3 and 4 are screen capture images from our genotype calling software. They are unbiased representations of the quality of the genotype clusters generated from the Illumina genotyping assay on a linkage set oligonucleotide pool (GS0005003-OPA). Separation between homozygote clusters is excellent and variation within a cluster is small. In fact, because there is such high precision within a cluster, linked polymorphisms are also captured by this assay. The second graph from the left on the bottom row shows potentially five clusters. Individuals falling into the lower purple cluster ("heterozygote") and the lower blue cluster ("homozygote") have a linked polymorphism under one of the ASOs. The allele frequency of the linked polymorphism is sufficiently low that no individuals in this panel of 96 individuals are homozygote for the linked polymorphism (hence no lower red cluster). This linked polymorphism has destabilized one of the ASOs and lowered the resultant assay intensity. This "extra" cluster phenomenon is analogous to the split peaks sometimes seen in STR analysis when a single base change in one of the repeats alters the normal migration pattern.

7. Genotyping performance

Various internal assay controls are used to assess the GoldenGate assay and array hybridization at various experimental steps, including gDNA/oligo annealing, PCR, array hybridisation, and imaging. For example, G/T or G/G mismatches; amplification balance of the

Fig. 4. GenCall software-produced plots of 10 randomly selected loci of 192 samples in Cartesian coordinate representation.

Table 1
Genotyping performance

	Reproducibility (%)	Heritability (%)	Call rate (%)	Assay development success rate (%)
Oligo pool 1: 1536 loci multiplex				
96 DNAs Run 1	100	100	99.96	93.68
96 DNAs Run 2	100	100	99.97	93.95
Oligo pool 2: 640 loci multiplex				
96 DNAs Run 1	100	99.99	100	93.91
96 DNAs Run 2	99.95	99.99	100	93.28

two types of universal PCR primers incorporated into the allele-specific oligos; hybridization controls; double label control to estimate optical balance of Cy3/Cy5 channels.

To estimate the impact of multiplexing level on genotyping performance, two oligo pools at two different multiplex levels (1536 and 640 loci) were run through the genotyping assay. These runs were performed in duplicate on 95 DNAs and a water control (not included in this analysis). The reproducibility was calculated from five duplicate samples among the 95 DNAs for all successfully developed assays in these two pools. The heritability was calculated from 35 trios among the 95 DNAs and is a measure determining whether the genotype calls follow Mendelian inheritance. The call rate is the fraction of genotypes called from among the total possible genotype calls for successfully genotyped DNAs. The assay development success rate is the fraction of assays actually functional from the total number of loci designed into the oligo pool.

As can be seen in Table 1, the reproducibility, heritability, and call rate are near 100%. The assay development success rate is at the low 90% level for these two particular oligo pools. Individual assay development success rate may vary and is highly dependent upon the SNPs selected and the informatics tools used to design the assay oligonucleotides. An international consortium of leading investigators (including Illumina scientists) has been formed to determine a haplotype map of the human genome using single nucleotide polymorphisms (HapMap project) [3]. The goal of the human HapMap project is to identify “tag” SNPs that may be used for linkage disequilibrium studies of complex genetic diseases. Illumina’s technology platform is being used to genotype over 60% of the SNP loci in the HapMap project. To date, 200,000 SNP assays have been developed using the BeadArray technology.

The GoldenGate genotyping assay has been in use in our service operations group for 2 years, and has proven to be a robust process that generates high quality data. Table 2 shows the assay success rate, genotype call rate, and DNA sample success rate from our service operations. A total of 28,850 DNA samples were run from various customers; 96.46% of them were successfully genotyped and high quality data returned to the customer. The genotyping assay is robust to variation in DNA quantity and quality. However, the genotyping assay is significantly compromised when less than 20% of the required input DNA is provided; a primary reason for the failure to successfully generate genotype calls was insufficient DNA quantity.

A total of 293,505 SNP loci were designed and oligonucleotides synthesized. 80.2% of the attempted assays were successful. The assay success rate is highly dependent upon the SNP loci selected. In many projects, the list of SNPs was fixed and assays had to be designed and synthesized, even though SNP loci may have scored poorly on our OligoDesigner software. Individual experience with assay success rate may vary

Table 2
Assay success rate, genotype call rate, and DNA sample success rate

	Total attempted	Total successful	Assays successfully developed (%)
Number of DNA samples	28850	27828	96.46
Number of SNP loci	293505	235391	80.20
Genotypes produced (DNA samples × SNP loci)	54111293	53969348	99.74

depending upon the choice of SNP loci. The genotypes produced or genotype call rate is a measure of the completeness of the generated data set. It is the number of delivered genotypes on successfully genotyped DNAs and successfully developed SNP assays. Illumina's highly multiplexed genotyping assay delivers a high call rate of 99.74%. In a blind study, conducted by independent third party, 26,850 genotypes were compared with Mass Spec data, and a 99.7% concordance was observed [13].

To measure the accuracy of the genotyping system in allele frequency estimation, a series of linear dilutions were performed between DNA samples of two individuals. The first concentration contained 100% Individual 1 (and 0% Individual 2), and the eighth concentration contained 0% Individual 1 (and 100% Individual 2). For each bead type (i.e., one SNP locus), Cy3 and Cy5 intensities (representing A and B alleles, respectively) were collected and extracted, using Illumina's imaging and image analysis system. The ratios of Cy3/(Cy3 + Cy5) and Cy5/(Cy3 + Cy5) were used as proxies for A-allele and B-allele frequencies, respectively. For each concentration, 12 repeated experiments were performed; each experiment was performed on a single fiber-bundle at 1170 multiplex. Of the total 1170 loci typed, 501 loci were found to have different genotypes between the two individuals. This subset of loci was used to estimate the accuracy of allele-frequency computations. For each locus, at each concentration, the sufficient statistics were computed. Based on these statistics, it was determined that on average, with 95% confidence, our technology can detect 8% difference in allele frequencies with a single experiment. This number can be significantly improved, if one further selects a subset of high-performing loci or measures the samples multiple times.

8. Adaptation of the methylation profiling assay to the SNP genotyping platform

Illumina is adapting the SNP genotyping system to high throughput DNA methylation detection, based on "SNP" genotyping of bisulfite-converted genomic DNA. In this assay, non-methylated cytosines (C) are converted to uracil (U) when treated with bisulfite, while methylated cytosines remain unchanged. Hybridization behavior of uracil is similar to that of thymine (T). The detection of the methylation status of a particular cytosine can thus be carried out using a genotyping assay for a C/T polymorphism. Methylation status of the interrogated locus can be determined by calculation of the ratio of the fluorescent signals from the "C" (methylated) and "T" (unmethylated) alleles. In a previous study [unpublished data], we successfully demonstrated the feasibility of DNA methylation profiling on fiber optic arrays and developed a controlled system for monitoring assay performance. We have established a standard process for probe design and data analysis, a standard bisulfite conversion protocol, and a set of internal controls and reference samples for assay development and calibration. Current assay sensitivity and specificity is shown to be sufficient to detect changes in methylation status at more than 100 different sites simultaneously, in 1 μg of human genomic DNA. A minimum of three levels of methylation can be distinguished at any single site: fully methylated, semi-methylated, and unmethylated. We are performing experiments to measure >1000 CpG sites simultaneously.

9. Adaptation of the gene expression profiling assay to the SNP genotyping platform

Illumina has developed a flexible, sensitive, accurate, and cost-effective gene expression profiling assay, dubbed the DASL™ assay (for cDNA-mediated annealing, selection, extension, and ligation) based on the same universal address array used for SNP genotyping [16]. In this assay, three oligos are designed to target a specific mRNA sequence in a way similar to the SNP assay design. If a sample contains a cDNA target (the RNA is converted to cDNA by random priming), the corresponding query oligos will bind to the cDNA, and become extended and ligated enzymatically. The ligated products are then amplified and fluorescently labeled during PCR, and finally detected by binding to address sequences on the array. The hybridization intensity is proportional to the original mRNA abundance in the sample and used to represent the expression level of the targeted transcripts.

The DASL assay multiplexes to 1536 sequence targets, i.e., 512 genes at three probes per gene. DASL is characterized by a dynamic range of 2.5–3 logs, using 100 ng total RNA, and a 1.3-fold difference

measurement precision. This results in a mid-density expression profiling system with high sample throughput, high sensitivity and fills a gap between two existing RNA profiling technologies: quantitative RT-PCR (high sample throughput/low gene content) and high-density oligo or cDNA microarray technology (high gene content/low sample throughput).

Due to its high sequence specificity, the DASL assay can be used for splice variant detection [17] as well as differential allele-specific expression monitoring (i.e., quantitative measuring the abundance of each allele of target gene transcripts) [13]. We have developed genotyping assays for 1152 cSNPs derived from 380 cancer related genes. Each assay target is chosen from the sense strand and within one exon, thus, they can be used to interrogate both genomic DNA and RNA. With this assay design, we are able to obtain not only genotype information at the genomic DNA level, but potentially differential allele-specific expression information as well. It is known that levels of gene transcripts originating from paternal and maternal chromosomes may differ, thus constituting the basis of differential allele expression. Inheritance of allelic expression levels may provide an important link between individual genetic variation and the origin of disease. In addition, comparison of allele expression profiles may facilitate the identification of dominant susceptibility alleles in case/control studies where the frequency of heterozygotes is higher in cases versus controls [18,19].

10. Discussion

One key aspect of the GoldenGate genotyping assay design is the incorporation of an address sequence, so that the assay products can be read out on a universal array [20–23]. The probes on the array are random, artificial sequences that are not SNP-specific. Any set of SNPs can be analyzed simply by building the address sequences into the SNP-specific assay oligonucleotides. The approach offers substantial flexibility. The universal probe set represented on the array comprises 1624 different sequences selected to not cross hybridize with each other or with sequences in the human genome. The use of a universal array greatly simplifies the manufacturing process and reduces costs.

Since we use a universal address sequence tagging approach, different address sequences can be assigned to the same SNP locus and used to interrogate the same SNP in different samples (pooled for hybridization). In this way, a single array could be used to analyze the same loci from different individuals. This pooling scheme can be quite useful for studies, which require genotyping large number of samples with relatively small SNPs (e.g., <100 SNPs). We have tested this scheme with an experimental design in which a set of 96 SNPs were associated with 10 discrete sets of 96 address sequences and used to genotype 10 samples in parallel, with readout on one array. We obtained exactly the same genotyping results using this pooling scheme as compared to that obtained with standard single-sample-single-array approach.

The GoldenGate assay can tolerate certain degree of DNA degradation. We have completed highly successful studies using DNA samples isolated from formalin-fixed, paraffin-embedded tissues (unpublished data) and whole genome amplified samples [24]. Formalin-fixed archival tissues represent an invaluable resource for genetic analysis, as they are the most widely available materials for studies of human diseases. The ability to perform genetic analysis in archived tissues, for which clinical follow-up is already available, will greatly facilitate research in correlating genetic profiles with clinical parameters, and eventually in developing biomarkers for therapeutic decision making.

Most recently, Illumina has developed an array-based whole genome genotyping (WGG) assay approach, which comprises a novel combination of well proven technologies (Gunderson et al., in preparation). It utilizes direct hybridization capture of processed genomic DNA to sequence-specific capture probes. After target capture, the SNP is genotyped by performing an array-based allele-specific primer extension reaction. After extension with labeled nucleotides and signal amplification the array is read out on a BeadArray Reader. Genotyping quality was demonstrated by assaying a set of HapMap SNPs, and the call rate and accuracy are similar to that of GoldenGate assay. This technology enables simultaneously genotyping hundreds of thousands of loci from a single sample without the need for PCR or ligation steps, significantly reducing labor and potential sample-handling errors, and the cost per data point. The number of SNPs that can be assayed from

one sample is limited only by the numbers of features on the array with unconstrained locus selection. Thus, it allows large-scale interrogation of variation in the human genome at many levels of resolution, accelerating the ability of researchers to cost-effectively unlock the genetic basis of disease. The new assay fulfills the growing need for fixed-content genotyping and complements the GoldenGate custom genotyping assay.

11. Summary

Our genotyping platform combines a highly efficient genotyping assay with high quality Sentrix Arrays to deliver unprecedented quality and throughput at a reasonable cost. The Illumina genotyping assay has demonstrated exceptional performance by measurements of: reproducibility, call rate, allelelic heritability, and assay development success rate. The scalability of the platform allows the user to perform small pilot studies or large scale SNP genotyping association studies under the same system for complex human genetic disease studies, pharmacogenomic applications, as well as rapid development of molecular diagnostics.

Acknowledgements

The authors thank Marc Laurent, Dale Yuzuki, Steve Barnard, Diping Che, Todd Rubano, Chanfeng Zhao, and Lixin Zhou for their dedicated efforts and contributions to the development of the SNP genotyping assay, bead chemistry, imaging systems, and image analysis tools, bioinformatics, and process automation. We thank Mark Chee and David Barker for their support and guidance for this work.

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Subject Re: 1-s2.0-S0027510705000278-main

From Monib Zirvi <matzirvi@yahoo.com>

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Date Apr 23, 2017 at 2:10 PM

Marina BIbikova is publishing papers with Jian Bing Fan to this day and likely knows where he is and how to contact him.

Sent from my iPhone

> On Apr 23, 2017, at 2:07 PM, Monib Zirvi <matzirvi@yahoo.com> wrote:
>
> Gunderson explicitly referencing Gerry, Barany et al (reference 20) for universal addressable (Zipcode) arrays
>
> <image1.png>
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> <1-s2.0-S0027510705000278-main.pdf>

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> Sent from my iPhone

View less

Post

John Carreyrou
@JohnCarreyrou

Theranos bought outside lab gear and tried to pass it off as its own in demos: suit wsj.com/articles/thera... via @WSJ

wsj.com
Theranos Secretly Bought Outside Lab Gear and Ran Fake Tests, Cour...

1:37 PM · 4/21/17 from Earth

Case 2:23-cv-01997-MCA-JSA Document 153 Filed 04/16/26 Page 1618 of 1679 PageID: 5718

Table 1. Hybridization Intensities of First and Second Sequences Resulting from the Different Activation/Attachment Chemistries for the Second Sequence

1st Sequence: S9 5′ (NH_2) TTTGATGTCCCATTCCCCACGCGTT 2nd Sequence: S13 5′ (NH_2 or CHO) TTTGATCGTAGCCGGTATGCGACGG					
immobilization chemistries for 2nd attachment	5A	5B	5C	5D	5E
hybridization intensity of the 1st sequence before the 2nd sequence was immobilized	4978	5100	5154	5120	4978
hybridization intensity of 1st sequence after the 2nd sequence was immobilized	3925	2640	2729	2852	2670
hybridization intensity of the 2nd sequence	808	205	457	430	2950
1st Sequence: S13 5′ (NH_2) TTTGATCGTAGCCGGTATGCGACGG 2nd Sequence: S9 5′ (NH_2 or CHO) TTTGATGTCCCATTCCCCACGCGTT					
immobilization chemistries for 2nd attachment	5A	5B	5C	5D	5E
hybridization intensity of the 1st sequence before the 2nd sequence was immobilized	3095	2872	2950	2930	3093
hybridization intensity of 1st sequence after the 2nd sequence was immobilized	2488	1500	1580	1550	1650
hybridization intensity of the 2nd sequence	1400	108	800	820	4800

beads in water (3 μm diameter, $\sim 5\times10^{10}$ bea
obtained from Bangs Laboratories, Inc., Carme
zation reagents, 3-aminopropyltrimethoxys
rcaptopropyltrimethoxysilane, and 3-glycidoxypr
hoxysilane were obtained from United Che
nologies (UCT), Bristol, PA. Succinimidyl 4-hy
otinate acetone hydrazone, and 5′-aldehyde mo
nucleotide 5′-(CHO) TTT GAA AAG CCT
CGG CGA A-3′ (capture probe) were obtained
nk, San Diego, CA. All other oligonucleotide
TTT GAA AAG GGA CGT GCG CTT CGA
re probe), 5′-HS-TTT GAA AAG GGA CGT
CGA A-3′ (capture probe), 5′-FAM-TTT CGC
GTA GGC TTT TCA A-3′ (target), 5′-FAM
AGC GCA CGT CCC TTT TCA A-3′ (target),
ed from Operon Technologies, Alameda, CA, o
ed in house using the Oligator™ technology
nucleotides were high performance liquid chrom
(HPLC) purified. All other reagents were obt

Subject Re: MonibZirviCornellvIllumina.docx

From Maria Kempe <maria.kempe@med.lu.se>

To: George Barany <barany@umn.edu>

Cc: Monib Zirvi <matzirvi@yahoo.com>, Valerie Cross Dorn <vlc1@cornell.edu>, Bob Hammer <rphammer@gmail.com>, Matthew Lubin <lubingenetics@me.com>, Pearson, Matthew <mpearson@akingump.com>, Jim Kahn <jkahn@med.cornell.edu>, Goldman, Michael <michael.goldman@leclairryan.com>, Francis Barany <barany@med.cornell.edu>, Carl F. Nathan <cnathan@med.cornell.edu>, Brian J Kelly <bjk44@cornell.edu>

Date Apr 23, 2017 at 2:30 PM

Dear George and All,

I was in George's lab when David Walt visited the university. I remember it very well. Walt was scheduled for meetings with faculty members and other researchers. I also met him and talked to him. I had ideas that his optic fibers could be molecularly imprinted (Incidentally, Walt took in a Spanish postdoc to do this more than a decade later. The postdoc came from a group in Madrid that I collaborated with in an EU-project 1999-2003. Irrelevant to the present case but a little interesting now when we discuss plagiarism: the Spanish group blatantly made a paper with themselves as sole authors on an HPLC-method fully developed in my lab). Anyway, back to the meeting with Walt: the meeting was in George's office. I have a copy of the email that George sent to Francis to introduce him to Walt. I found the email after I had submitted all the documents in 2015. I told Angela about it when I

was in New York for the deposition and asked if it was relevant and if I should submit it, but was told it was not. Anyway, I still have it. I am not at home

was not. Anyway, I still have it. I am not at home right now, but can send it later today when I have access to my computer.

Best regards,
Maria

Sent from my iPad

On 23 Apr 2017, at 15:30, George Barany <barany@umn.edu> wrote:

> Dear All,
>
> I have carefully read Monib's declaration, and compared it to my own recollections and understanding of the case. Monib makes numerous compelling points that, in my opinion, should be deeply troubling to any fair-minded judge once called to his or her attention through an appropriate mechanism. It has been explained to me that this is better done by parties with direct standing, which would specifically be Cornell rather than one (or more) of the inventors.
>
> Two more points on which I can comment directly. (1) I distinctly remember Fodor's participation in the site visit that reviewed our program project grant, and the snide way in which, off-the-record, he "damned with faint praise" the chemistry section of the proposal that I was PI on; this may have included the universal array concept. (2) As I revealed to Matthew Pearson's team in preparing for the deposition (you'll have to review the transcript to see if it actually came up), I played "matchmaker" to introduce Francis to David Walt. I had met Walt when he gave a seminar at the U of M about his fiber optics connected to the artificial nose project, and realized that there might be common interests and possibilities involving DNA recognition (I don't remember the exact timeline, though I suspect it could be reconstructed fairly easily).
>
> I hope these remarks are helpful, even as we are very short on time with the judge about to conduct a final review of the proposed settlement terms.

Best wishes,

GB

On Sat, Apr 22, 2017 at 9:58 PM, Monib Zirvi
<matzirvi@yahoo.com> wrote:

> I had written up a declaration that I was going to send to Judge Stark with the help of an attorney. If you can take the time to read it, I would greatly appreciate it.
>
> Sent from my iPhone

--
George Barany
Distinguished McKnight University Professor of Chemistry
University of Minnesota
Department of Chemistry
[redacted]

View less

Subject Re: Private & Confidential Re: Updated Markman Deck, p1-29

From Francis Barany <barany@med.cornell.edu>

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Date Apr 23, 2017 at 2:47 PM

Dear Team,

Thank you for your additional comments and vote of support. The "High-throughput SNP genotyping on universal bead arrays" paper (just sent my Monib, and re-enclosed) could not make the literal infringement any clearer.

I am providing an updated deck that highlights infringement, in case the Infinium Arrays were synthesized as described in the Steinberg-Tatman paper. The deck is in 3 parts.

(I am also sending a private email response to the Cornell only team.)

Best,

Francis

[redacted]
barany@med.cornell.edu

[redacted]

On Apr 22, 2017, at 7:07 PM, Francis Barany <barany@med.cornell.edu> wrote:

Dear Team,

Monib found another document from Illumina that contains our zip codes, published in 2004.

A few points to put in perspective:

1. This was a bit harder to find, since the presence of spaces requires a more sophisticated Google Search.

2. Once again, the Steinberg paper copies 2 of our zip codes, probability that they would pick these two sequences randomly is: 7.9 x 10 ee 28th. These zip codes have identical tetramers in positions 1, 2, & 6, thus making them very close in sequence, which is what you want in order to test conditions that minimize cross-hybridizations ??? exactly as taught in the '917 patent.

3. The Steinberg 2004 paper picked the FRIST TWO Zipcodes they plagiarized from the Barany/Zirvi set. The Seinberg-Tatmann 2006 paper picked the THIRD and FOURTH Zipcodes. This is not an accident.

4. Maria and George, you may find the chemistry described in these papers interesting, as I do

believe you described most of it in the ???917 patent application.

(I am also sending a private email to the Cornell only team.)

Best,

Francis

[redacted]
barany@med.cornell.edu

[redacted]

<Covalent_attachment_DNA_Beads_Steinberg_2004_v02.pdf>

<Covalent_attachment_DNA_Beads_Steinberg_2004_M&M.tiff>

> On Apr 22, 2017, at 10:11 AM, Maria Kempe <maria.kempe@med.lu.se> wrote:
>
> Dear All,
>
> Thanks for the call yesterday.
> Francis: you have my full trust.
> Monib: thanks for your great efforts and input, they are appreciated.
>
> Best regards,
> Maria
>
> Sent from my iPad
>
> On 22 Apr 2017, at 14:21, Francis Barany <barany@med.cornell.edu> wrote:
>
>> Dear Monib, fellow inventors, Matthew P., and Cornell Team,
>>
>> Monib - excellent sleuthing.
>>
>> In fact, BOTH sequences listed are from the 16 Barany/Zirvi zip-codes.
>>
>> (Illumina adds an extra ???T??? base on the 5??? end ??? this is an insignificant and

5 : : : end : : : this is an insignificant and inconsequential addition).

The probability that they would pick thees two sequences randomly is: 7.9 x 10 ee 28th ??? or essentially the same as 1 in the total number of stars in the universe. In other words ??? impossible.

Inventors, in order that I do not inadvertently violate privilege I will communicate with Valerie and the Cornell Team privately. I do hope that you trust that I am trying my best to represent all the inventors interests.

But now, I need to run some errands and then go to the March for Science (NYC).

Best,

Francis

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

On Apr 22, 2017, at 12:27 AM, Monib Zirvi <matzirvi@yahoo.com> wrote:

Search this Illumina publication for
This Barany/Zirvi Zipcode:

TTTGATCGTAGCCGGTATGCGACGG

Sent from my iPhone
<bc060012v.pdf>

<Synthetic Modification Silica Beads Illumina

2006_Table1.tiff>

View less

Markman Cornell Illumina _04_23_2017…

High-throughput SNP genotyping on uni…

Subject Re: Private & Confidential Re: Updated Markman Deck, p30-71

From Francis Barany <barany@med.cornell.edu>

To: Valerie Cross <vlc1@cornell.edu>, mpearson@akingump.com <mpearson@akingump.com>, bjk44@cornell.edu <bjk44@cornell.edu>, James R. Kahn <jkahn@med.cornell.edu>, Maria Kempe <maria.kempe@med.lu.se>, Monib Zirvi <matzirvi@yahoo.com>, rphammer@gmail.com <rphammer@gmail.com>, lubingenetics@me.com <lubingenetics@me.com>, George Barany <barany@umn.edu>, Michael Goldman <michael.goldman@leclairryan.com>, Carl F. Nathan <cnathan@med.cornell.edu>

Date Apr 23, 2017 at 2:48 PM

Part 2.

Francis

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

Markman Cornell Illumina _04_23_2017…

Subject Re: MonibZirviCornellvIllumina.docx

From Monib Zirvi <matzirvi@yahoo.com>

To: Maria Kempe <maria.kempe@med.lu.se>

Cc: George Barany <barany@umn.edu>, Valerie Cross Dorn <vlc1@cornell.edu>, Bob Hammer <rphammer@gmail.com>, Matthew Lubin <lubingenetics@me.com>, Pearson, Matthew <mpearson@akingump.com>, Jim Kahn <jkahn@med.cornell.edu>, Goldman, Michael <michael.goldman@leclairryan.com>, Francis Barany <barany@med.cornell.edu>, Carl F. Nathan <cnathan@med.cornell.edu>, Brian J Kelly <bjk44@cornell.edu>

Date Apr 23, 2017 at 2:49 PM

That sounds very relevant to me.

Monib

Sent from my iPhone

On Apr 23, 2017, at 1:58 PM, Maria Kempe <maria.kempe@med.lu.se> wrote:

Dear George and All,

I was in George's lab when David Walt visited the university. I remember it very well. Walt was scheduled for meetings with faculty members and other researchers. I also met him and talked to him. I had ideas that his optic fibers could be molecularly imprinted (Incidentally, Walt took in a Spanish postdoc to do this more than a decade later. The postdoc came from a group in Madrid that I collaborated with in an EU-project 1999-2003.

Irrelevant to the present case but a little interesting now when we discuss plagiarism: the Spanish group blatantly made a paper with themselves as sole

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On 23 Apr 2017, at 15:30, George Barany <barany@umn.edu> wrote:

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Best wishes,

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Distinguished McKnight University Professor of Chemistry
University of Minnesota
Department of Chemistry
[redacted]

View less

Subject Re: MonibZirviCornellvIllumina.docx

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Cc: George Barany <barany@umn.edu>, Valerie Cross Dorn <vlc1@cornell.edu>, Bob Hammer <rphammer@gmail.com>, Matthew Lubin <lubingenetics@me.com>, Pearson, Matthew <mpearson@akingump.com>, Jim Kahn <jkahn@med.cornell.edu>, Goldman, Michael <michael.goldman@leclairryan.com>, Francis Barany <barany@med.cornell.edu>, Carl F. Nathan <cnathan@med.cornell.edu>, Brian J Kelly <bjk44@cornell.edu>

Date Apr 23, 2017 at 2:50 PM

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Thank you

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George Barany
Distinguished McKnight University Professor of Chemistry
University of Minnesota
Department of Chemistry
[redacted]

View less

Subject Re: Private & Confidential Re: Updated Markman Deck, p72-122

From Francis Barany <barany@med.cornell.edu>

To: Valerie Cross <vlc1@cornell.edu>, mpearson@akingump.com <mpearson@akingump.com>, bjk44@cornell.edu <bjk44@cornell.edu>, James R. Kahn <jkahn@med.cornell.edu>, Maria Kempe <maria.kempe@med.lu.se>, Monib Zirvi <matzirvi@yahoo.com>, rphammer@gmail.com <rphammer@gmail.com>, lubingenetics@me.com <lubingenetics@me.com>, George Barany <barany@umn.edu>, Michael Goldman <michael.goldman@leclairryan.com>, Carl F. Nathan <cnathan@med.cornell.edu>

Date Apr 23, 2017 at 2:51 PM

Part 3.

Please confirm receipt.

Francis

[redacted]

barany@med.cornell.edu

[redacted]

Markman Cornell Illumina _04_23_2017…

Subject Re: Private & Confidential Re: Updated Markman Deck, p72-122

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To: Francis Barany <barany@med.cornell.edu>

Cc: Valerie Cross <vlc1@cornell.edu>, mpearson@akingump.com <mpearson@akingump.com>, bjk44@cornell.edu <bjk44@cornell.edu>, James R. Kahn <jkahn@med.cornell.edu>, Maria Kempe <maria.kempe@med.lu.se>, Monib Zirvi <matzirvi@yahoo.com>, rphammer@gmail.com <rphammer@gmail.com>, lubingenetics@me.com <lubingenetics@me.com>, Michael Goldman <michael.goldman@leclairryan.com>, Carl F. Nathan <cnathan@med.cornell.edu>

Date Apr 23, 2017 at 3:33 PM

Confirming receipt of all three, and appreciative of the enormous amount of work that went into preparing these materials. GB

On Sun, Apr 23, 2017 at 1:48 PM, Francis Barany <barany@med.cornell.edu> wrote:

> Part 3.
>
> Please confirm receipt.
>
> Francis
>
> [redacted]
>
> barany@med.cornell.edu
>
> [redacted]

View less

--
George Barany
Distinguished McKnight University Professor of
Chemistry
University of Minnesota
Department of Chemistry
[redacted]

Subject Re: MonibZirviCornellvIllumina.docx

From Maria Kempe <maria.kempe@med.lu.se>

To: Monib Zirvi <matzirvi@yahoo.com>

Cc: George Barany <barany@umn.edu>, Valerie Cross Dorn <vlc1@cornell.edu>, Bob Hammer <rphammer@gmail.com>, Matthew Lubin <lubingenetics@me.com>, Pearson, Matthew <mpearson@akingump.com>, Jim Kahn <jkahn@med.cornell.edu>, Goldman, Michael <michael.goldman@leclairryan.com>, Francis Barany <barany@med.cornell.edu>, Carl F. Nathan <cnathan@med.cornell.edu>, Brian J Kelly <bjk44@cornell.edu>

Date Apr 23, 2017 at 5:31 PM

Dear All,

I am sending copies of two emails, from April and May 1995, describing Francis initial contacts with Walt.

Best regards,
Maria

From: Monib Zirvi <matzirvi@yahoo.com>
Sent: Sunday, April 23, 2017 8:50 PM
To: Maria Kempe
Cc: George Barany; Valerie Cross Dorn; Bob Hammer; Matthew Lubin; Pearson, Matthew; Jim Kahn; Goldman, Michael; Francis Barany; Carl F. Nathan; Brian J Kelly
Subject: Re: MonibZirviCornellvIllumina.docx

Dear Maria,

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Thank you

Monib

Sent from my iPhone

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> Sent from my iPhone

--
George Barany
Distinguished McKnight University Professor of Chemistry
University of Minnesota
Department of Chemistry
[redacted]

View less

Email - 950427.pdf

Email - 950501.pdf

Date: Thu, 27 Apr 1995 13:14:15 -0500 (CDT)
From: George Barany <barany@maroon.tc.umn.edu>
To: Maria Kempe <kempe@chemsun.chem.UMN.EDU>,
Ioana Stoenescu <stoen002@gold.tc.umn.edu>
Cc: Francis Barany <barany@mail.med.cornell.edu>
Subject: David Walt (fwd)

dear maria and ioana, now my brother called walt and here is his report. as you can see, lots of different options will be tried to prove the zip-code array concepts. GB

ps what do you think is best functional group for surface prior to attaching the oligo or the PNA??

---------- Forwarded message ----------
Date: Thu, 27 Apr 1995 12:19:04 -0400
From: Francis Barany <barany@mail.med.cornell.edu>
To: barany@maroon.tc.umn.edu, chammer@sn01.sncc.lsu.edu,
dbergstr@mace.cc.purdue.edu
Cc: hjblok@mail.med.cornell.edu
Subject: David Walt

Dear All,

I spoke with David Walt yesterday, Chairman of Chemistry at Tufts.

He has developed optical fiber sensor arrays. By using a microscope, he can focus a macroscopic mask on one end of a fiber, so the other end will have a miniature version of the mask. The light activates polymerization on the tip - which is how he links on enzymes or other goodies.

The tremendous advantage of this approach is the ability to deposit a three dimensional matrix at an appropriate address, and this can give far greater loadings than just a straight glass surface. The disadvantage is that it may give the same kind of problems as a membrane.

David said he could functionalixe any way we want. George recommends putting COOH groups on the end. Then we can make a peptide link with water soluble carbodiimide Any other suggestions??

David W. will prepare some spots for Herman Blok to test with radioactivity, and if that works, we can go to fluorescent detection.

Meanwhile, independent of whether this fiberoptic trick and polymer approach is an improvement, we will still need improved chemistries for linking oligos to the surface. Ultimately, we will need to get this to work with PNA. The more I think about it, I realize how superior the PNA tetramer is.

Take care,

Francis

Date: Mon, 1 May 1995 17:13:04 -0400
From: Francis Barany <barany@mail.med.cornell.edu>
To: dwalt@pearl.tufts.edu
Cc: barany@maroon.tc.umn.edu, chammer@sn01.sncc.lsu.edu,
dbergstr@mace.cc.purdue.edu, hjblok@mail.med.cornell.edu
Subject: Derivatized Glass

Dear David,

It was a pleasure to speak with you last week. You will be receiving a FedEx package from me some time this week which will include a confidential copy of our zip code approach, and some special glass slides for making the first test systems. These glass slides are a special thickness and will be used in a Perkin Elmer In-Situ PCR machine. I haven't received the slides yet, but as soon as I do, they will be sent to you.

I have discussed with my co-workers what type of functionality we would like on the polyethylene surfaces you can place on specific regions of glass using your optic fiber system. The early consensus is a COOH group so we can link it to our Amino-link oligonucleotides using water soluble carbocarbodi-imide activation. I'm not quite sure of the efficiency of this reaction, so I was wondering if you could make an activated group directly on your surface, so I could just react the amino-link oligo directly to your group. Perhaps you have some other suggestions. The COOH group will ultimately be used for building arrays using PNA oligomers on the surface.

I would also like to provide you with the phone numbers and E.mail addresses of the other collaborators on the zip code capture team:

Francis Barany,	212-746-6509,	barany@mail.med.cornell.edu
George Barany,	612-625-1028,	barany@maroon.tc.umn.edu
Donald Bergstrom,	317-494-6275,	dbergstr@mace.cc.purdue.edu
Herman Blok,	212-746-6507,	hjblok@mail.med.cornell.edu
Robert Hammer,	504-388-4025,	chammer@sn01.sncc.lsu.edu

I'm looking forward to collaborating with you.

Francis

Subject Re: Private & Confidential Re: Updated Markman Deck, p72-122

From Robert Hammer <rphammer@gmail.com>

To: George Barany <barany@umn.edu>

Cc: Francis Barany <barany@med.cornell.edu>, Valerie Cross <vlc1@cornell.edu>, mpearson@akingump.com <mpearson@akingump.com>, bjk44@cornell.edu <bjk44@cornell.edu>, James R. Kahn <jkahn@med.cornell.edu>, Maria Kempe <maria.kempe@med.lu.se>, Monib Zirvi <matzirvi@yahoo.com>, lubingenetics@me.com <lubingenetics@me.com>, Michael Goldman <michael.goldman@leclairryan.com>, Carl F. Nathan <cnathan@med.cornell.edu>

Date Apr 23, 2017 at 5:33 PM

I confirm receipt

bob

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> > Part 3.
> >
> > Please confirm receipt.
> >
> > Francis
> >
> > [redacted]

[redacted]

barany@med.cornell.edu

[redacted]

--

George Barany
Distinguished McKnight University Professor of Chemistry
University of Minnesota
Department of Chemistry

[redacted]

View less

Subject Re: MonibZirviCornellvIllumina.docx

From Monib Zirvi <matzirvi@yahoo.com>

To: Maria Kempe <maria.kempe@med.lu.se>

Cc: George Barany <barany@umn.edu>, Valerie Cross Dorn <vlc1@cornell.edu>, Bob Hammer <rphammer@gmail.com>, Matthew Lubin <lubingenetics@me.com>, Pearson, Matthew <mpearson@akingump.com>, Jim Kahn <jkahn@med.cornell.edu>, Goldman, Michael <michael.goldman@leclairryan.com>, Francis Barany <barany@med.cornell.edu>, Carl F. Nathan <cnathan@med.cornell.edu>, Brian J Kelly <bjk44@cornell.edu>

Date Apr 23, 2017 at 6:04 PM

That looks very important to me.

Monib

Sent from my iPhone

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University of Minnesota
Department of Chemistry
[redacted]

[redacted]

<Email - 950427.pdf>
<Email - 950501.pdf>

View less

Subject Confidential Zip Code Approach

From Monib Zirvi <matzirvi@yahoo.com>

To: Valerie Cross Dorn
<vlc1@cornell.edu>,
<rphammer@gmail.com>,
<lubingenetics@me.com>,
<mpearson@akingump.com>,
<maria.kempe@med.lu.se>,
<jkahn@med.cornell.edu>,
<michael.goldman@leclairryan.com>,
<barany@umn.edu>,
<barany@med.cornell.edu>,
<cnathan@med.cornell.edu>,
<bjk44@cornell.edu>

Date Apr 23, 2017 at 6:12 PM

Seems pretty clear that DMAP dll files still contain "confidential" Zipcodes all these years later

Sent from my iPhone

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From Maria Kempe <maria.kempe@med.lu.se>

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Date Apr 23, 2017 at 6:14 PM

Dear Francis,

I confirm the receipt of all three documents + the Shen et al. paper.

Best regards,
Maria

From: Francis Barany <barany@med.cornell.edu>
Sent: Sunday, April 23, 2017 8:48 PM
To: Valerie Cross; mpearson@akingump.com; bjk44@cornell.edu; James R. Kahn; Maria Kempe; Monib Zirvi; rphammer@gmail.com; lubingenetics@me.com; George Barany; Michael Goldman; Carl F. Nathan

Subject: Re: Private & Confidential Re: Updated Markman Deck, p72-122

Part 3.

Please confirm receipt.

Francis

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

View less

Subject Re: Private & Confidential Re: Updated Markman Deck, p72-122

From Valerie Cross Dorn <vlc1@cornell.edu>

To: Francis Barany <barany@med.cornell.edu>

Cc: Matt Pearson <mpearson@akingump.com>, Brian Kelly <bjk44@cornell.edu>, Jim Kahn <jkahn@med.cornell.edu>, Maria Kempe <maria.kempe@med.lu.se>, Monib Zirvi <matzirvi@yahoo.com>, rphammer@gmail.com <rphammer@gmail.com>, lubingenetics@me.com <lubingenetics@me.com>, George Barany <barany@umn.edu>, Michael Goldman <michael.goldman@leclairryan.com>, Carl F. Nathan <cnathan@med.cornell.edu>

Date Apr 23, 2017 at 9:34 PM

Francis, I am confirming receipt but believe this is not new analysis. We have evaluated it already.
Valerie

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>
> Part 3.
>
> Please confirm receipt.
>
> Francis
>
> [redacted]
>
> barany@med.cornell.edu
>
> [redacted]

<Markman Cornell Illumina
_04_23_2017_v04_p72-122.pdf>

View less

Subject Re: MonibZirviCornellvIllumina.docx

From Valerie Cross Dorn <vlc1@cornell.edu>

To: Monib Zirvi <matzirvi@yahoo.com>

Cc: rphammer@gmail.com <rphammer@gmail.com>, lubingenetics@me.com <lubingenetics@me.com>, Matt Pearson <mpearson@akingump.com>, maria.kempe@med.lu.se <maria.kempe@med.lu.se>, Jim Kahn <jkahn@med.cornell.edu>, michael.goldman@leclairryan.com <michael.goldman@leclairryan.com>, barany@umn.edu <barany@umn.edu>, barany@med.cornell.edu <barany@med.cornell.edu>, cnathan@med.cornell.edu <cnathan@med.cornell.edu>, Brian Kelly <bjk44@cornell.edu>

Date Apr 23, 2017 at 9:44 PM

Monib, you have included information that is not consistent with the history of the case and you are not authorized by Cornell to submit this. Valerie

> On Apr 22, 2017, at 10:58 PM, Monib Zirvi <matzirvi@yahoo.com> wrote:
>
> I had written up a declaration that I was going to send to Judge Stark with the help of an attorney. If you can take the time to read it, I would greatly appreciate it.
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Date Apr 23, 2017 at 9:58 PM

Dear Valerie,

I believe you are mistaken. Other inventors have recollections consistent with this. I understand that Cornell did not authorize sending the declaration, thus I have not sent it.

I believe some of the information contained is very important for any Judge to make a fair decision, and I hope Cornell fully informs Judge Stark of these issues.

Sincerely,

Monib

Sent from my iPhone

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Date Apr 23, 2017 at 10:06 PM

There are new figures based on the Steinberg 2006 infinium addresses in the update.

Monib

Sent from my iPhone

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Date Apr 23, 2017 at 10:28 PM

Dear Valerie,

Thank you for confirming receipt of the deck.

New slides were added to help illustrate that even with the Markman wording:

(i) We have proven literal infringement of the zip code arrays used in the Goldengate assays, the DASL assays, the MicroRNA expression assay, and the Gene Expression assays. Please focus on pages 81, 84, 90, 91, 92, & 93.

In addition, enclosed are two Excel files, comprising 1,493 and 1,536 Illumicodes, used on universal zip code bead arrays in GoldenGate (and presumably other Illumina assays) that ALL LITERALLY infringe on the Barany '917 family of patents as per the Markman wording.

(ii) We have given compelling and new analysis

(ii) We have given compelling and new analysis showing the doctrine of equivalents for infringement of the Infinium chips, based on the Steinberg-Tatman 2006 paper, if that is the design currently used by Illumina, as implied by the current Scripps vs. Illumina case. Please focus on pages 110-121.

We believe there is overwhelming evidence that Cornell is being infringed upon in the first set of products, and those products alone are reason enough to continue onward so the world will learn the truth. It was my understanding of the confidential April 12th meeting that both Akin Gump and Latham Watkins were in agreement with the facts concerning part (i) above.

We understand that with regards to the Infinium products (part (ii)) there are certain details that we don't know because they are covered by the protective order. Thus, the inventors respectfully request an impartial outside review of the facts by a qualified team which already has access to the confidential information in the protective order due to past and ongoing legal actions against Illumina array products.

Valerie, I have written separately to you on behalf of the inventors and I do hope you will consider a pause, such that all the options in front of you are fairly evaluated.

Most appreciated,

Francis

[redacted]
[redacted]
barany@med.cornell.edu

[redacted]

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[redacted]

<Markman Cornell Illumina
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Illumina Golden Gate Assay Primer Pro…

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Subject Re: MonibZirviCornellvIllumina.docx

From Valerie Cross Dorn <vlc1@cornell.edu>

To: Monib Zirvi <matzirvi@yahoo.com>

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Date Apr 24, 2017 at 8:06 AM

Monib, the issues with your proposed declaration related to what transpired in the case, not what the inventors recollect.

We have already explained to you the initial disclosures served by Illumina that listed JB Fan, that were amended to remove him (which Illumina had the procedural right to do), and plaintiffs' independent efforts to depose him without success. We have also explained that we obtained from Illumina witnesses duly designated on their initial disclosures all of the information we sought about operation of the products accused of infringing in this case. Mark Chee was not listed on Illumina's initial disclosures and we did not seek to depose him. Your inclusion of incorrect facts undermines the points you are trying to make, and it is important to highlight here that your points relate not to proving infringement in this case, but to establishing other actions of Illumina with which you find fault

other actions of Illumina with which you find fault.

For these reasons, we continue to decline to authorize you to file this document or anything like it in connection with Cornell's legal rights asserted in this case. Thank you for sending it for us to consider, and for confirming that you have not sent it to the court. I want to assure you that we have considered the points you have been raising over the past 4 months, and we have tried to explain to you how those points may or may not impact the claims in this case.

In the event further discussion is necessary, we will consider scheduling another conference call.

Valerie

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Date Apr 24, 2017 at 8:15 AM

My contention is that Mark Chee and Jian Bing Fan are important witnesses and it appears that Illumina may have been aware of their locations on multiple occasions.

Monib

Sent from my iPhone

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> >
> > Sent from my iPhone
> > <MonibZirviCornellvIllumina.docx.pdf>

View less

Subject Confidential

From Pearson, Matthew <mpearson@AKINGUMP.com>

To: Francis Barany <barany@med.cornell.edu>, George Barany <barany@umn.edu>, Robert Hammer <rphammer@gmail.com>, lubingenetics@me.com <lubingenetics@me.com>, Maria Kempe <maria.kempe@med.lu.se>, Monib Zirvi <matzirvi@yahoo.com>

Cc: Jim Kahn <jkahn@med.cornell.edu>, Brian Kelly <bjk44@cornell.edu>, Valerie Cross Dorn <vlc1@cornell.edu>

Date Apr 24, 2017 at 8:20 PM

Dear All –

First - thank you all for your attention during the call last Friday.

Second - I have attached the order from Judge Stark today. The docket entry is included in the email below.

Docket Text:
SO ORDERED, re [596] Joint Stipulation to Dismiss, ***Civil Case Terminated. Signed by Judge Leonard P. Stark on 4/24/17. (ntl)

Matthew A. Pearson
AKIN GUMP STRAUSS HAUER & FELD LLP
[redacted] 19103-7013 | USA | Direct: +1 215.965.1258 | Internal: 21258
Fax: +1 215.965.1210 | mpearson@akingump.com | akingump.com | Bio

2017-04-24 Order - Docket Item 598.pdf

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

CORNELL UNIVERSITY, CORNELL RESEARCH FOUNDATION, INC., LIFE TECHNOLOGIES CORPORATION, and APPLIED BIOSYSTEMS, LLC,	)	
Plaintiffs,	)	
v.	)	C.A. No. 10-433-LPS-MPT
ILLUMINA, INC.,	)	
Defendant.	)	

JOINT STIPULATION TO DISMISS

IT IS HEREBY STIPULATED AND AGREED, by and between the parties hereto, through their respective counsel, that:

1. Pursuant to Rule 41(a)(1)(A)(ii) of the Federal Rules of Civil Procedure, all claims asserted by Plaintiffs against Defendant are hereby dismissed with prejudice and all counterclaims asserted by Defendant against Plaintiffs are hereby dismissed without prejudice.

2. Plaintiffs' Fee Submission (D.I. 459) is hereby withdrawn.

3. Each party shall bear its own fees and costs.

SO STIPULATED this 18th day of April, 2017.

/s/ Karen E. Keller
John W. Shaw (No. 3362)
Karen E. Keller (No. 4489)
David M. Fry (No. 5486)
SHAW KELLER LLP
300 Delaware Avenue, Suite 1120
Wilmington, DE 19801
(302) 298-0700
jshaw@shawkeller.com
kkeller@shawkeller.com
dfry@shawkeller.com
Attorneys for Plaintiffs

/s/ Steven J. Balick
Steven J. Balick (No. 2114)
Andrew C. Mayo (No. 5207)
ASHBY & GEDDES
500 Delaware Avenue, 8th Floor
P.O. Box. 1150
Wilmington, DE 19899
(302) 654-1888
sbalick@ashby-geddes.com
amayo@ashby-geddes.com
Attorneys for Defendant

SO ORDERED this 24th day of April, 2017.

United States ~~Magistrate~~ Judge

Date: Mon, 1 May 1995 17:13:04 -0400
From: Francis Barany <barany@mail.med.cornell.edu>
To: dwalt@pearl.tufts.edu
Cc: barany@maroon.tc.umn.edu, chammer@sn01.sncc.lsu.edu,
dbergstr@mace.cc.purdue.edu, hjblok@mail.med.cornell.edu
Subject: Derivatized Glass

Dear David,

It was a pleasure to speak with you last week. You will be receiving a FedEx package from me some time this week which will include a confidential copy of our zip code approach, and some special glass slides for making the first test systems. These glass slides are a special thickness and will be used in a Perkin Elmer In-Situ PCR machine. I haven't received the slides yet, but as soon as I do, they will be sent to you.

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From: Francis Barany <barany@mail.med.cornell.edu>
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Cc: barany@maroon.tc.umn.edu, chammer@sn01.sncc.lsu.edu,
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I have discussed with my co-workers what type of functionality we would like on the polyethylene surfaces you can place on specific regions of glass using your optic fiber system. The early consensus is a COOH group so we can link it to our Amino-link oligonucleotides using water soluble carbocarbodi-imide activation. I'm not quite sure of the efficiency of this reaction, so I was wondering if you could make an activated group directly on your surface, so I could just react the amino-link oligo directly to your group. Perhaps you have some other suggestions. The COOH group will ultimately be used for building arrays using PNA oligomers on the surface.

I would also like to provide you with the phone numbers and E.mail addresses of the other collaborators on the zip code capture team:

Francis Barany,	212-746-6509,	barany@mail.med.cornell.edu
George Barany,	612-625-1028,	barany@maroon.tc.umn.edu
Donald Bergstrom,	317-494-6275,	dbergstr@mace.cc.purdue.edu
Herman Blok,	212-746-6507,	hjblok@mail.med.cornell.edu
Robert Hammer,	504-388-4025,	chammer@sn01.sncc.lsu.edu

I'm looking forward to collaborating with you.

Francis